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RING OPENING OF CYCLOPROPYLCARBINYL RADICALS AND PRELIMINARY STUDIES ON THE SYNTHESIS OF CALICHEAMICINONE

by

SYLVAIN DAIGNEAULT

A THESIS
SUBMITED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
Spring 1991

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To whom it may concern

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Professor of Chemistry

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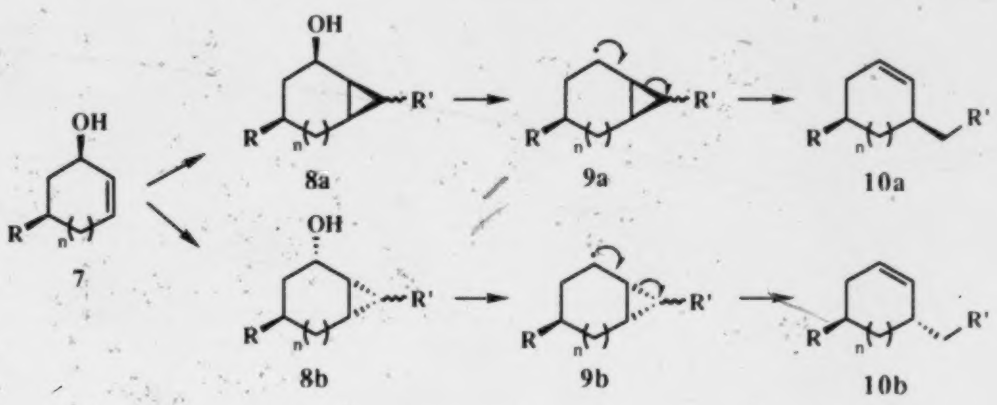
Cette thèse est dédiée à Christine et à ma famille

ABSTRACT

This thesis deals with two subjects: Ring opening of cyclopropylcarbinyl radicals as a synthetic methodology, and synthetic studies related to Calicheamicinone.

In the first chapter, cyclopropylcarbinols **8a** and **8b** (Scheme A), which are accessible by a number of routes, are converted into the corresponding radicals **9a** and **9b**, respectively. These radicals undergo peripheral ring-opening of the cyclopropyl substructure to afford substituted cycloalkenes **10a** and **10b**. The whole sequence represents a general method for attaching alkyl, and substituted alkyl groups to an existing cyclic structure and it can often be carried out with predictable stereo- and regiochemical control.

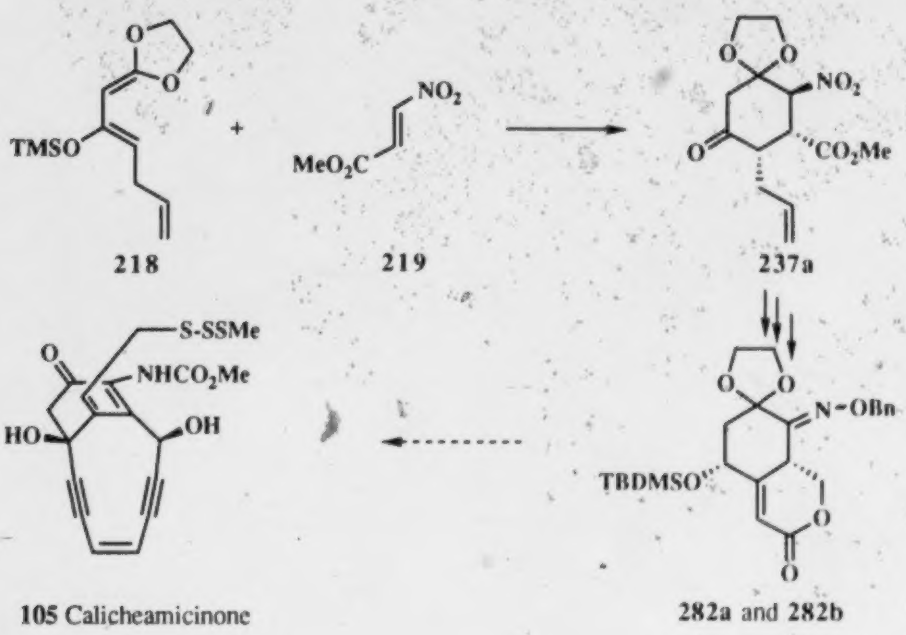
SCHEME A



This new methodology was then combined with conventional radical ring closure for the preparation of benzofuran derivatives needed for evaluation as inhibitors of leukotriere biosynthesis.

In the second chapter, synthetic studies related to the aglycon portion (calicheamicinone) **105** of the newly-discovered antitumor agent calicheamicin $\gamma_1{}^I$ is described.

SCHEME B



TMSO
O
O
+
NO2
MeO2C
218
219
O
O
NO2
O
CO2Me
237a
S-SSMe
O
NHCO2Me
HO
OH
105 Calicheamicinone
O
O
N-OBn
TBDMSO
O
O
282a and 282b

The central core of **105** was constructed by a Diels-Alder cycloaddition involving the novel diene **218** and the known dienophile **219** (Scheme B). Further elaboration of the resulting cyclohexanone **237a** led to the advanced intermediates **282a** and **282b**.

In addition to describing our own synthetic work, the second chapter reviews the published synthetic achievements of other researchers in this field.

ACKNOWLEDGEMENTS

I express my gratitude to Professor D.L.J. Clive for his advice and encouragement throughout the course of my studies, and for his assistance in the preparation of this manuscript.

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Finally, I thank Christine, for her patience, support, and understanding throughout the course of this work.

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LIST OF ABREVIATIONS

A	adenine
Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
Ar	aryl
Bn	benzyl
Bz	benzoyl
Bu	butyl
t-Bu	*tertiary*-butyl
C	cytidine
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[4.3.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	*N,N*-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
Et	ethyl
FMOC	9-fluorenylmethyl chloroformate
G	guanine
HMPA	hexamethylphosphoramide
HOMO	highest-energy occupied molecular orbital
Im	imidazole
KHMDS	potassium hexamethyldisilazide
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LUMO	lowest-energy unoccupied molecular orbital
MCPBA	*meta*-chloroperbenzoic acid
MEM	methoxyethoxymethyl

LIST OF ABREVIATIONS (Cont'd)

Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMMO	*N*-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
Ph	phenyl
Phth	phthaloyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
i-Pr	isopropyl
pyr	pyridine
SOMO	singly occupied molecular orbital
T	thymidine
TBAF	tetrabutylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
Tf	triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
Thexyl	1,1,2-trimethylpropyl
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

CHAPTER 1

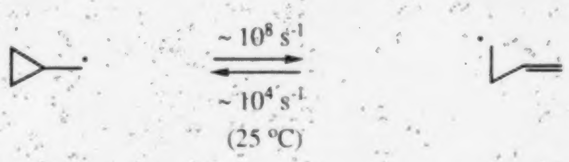
SYNTHETIC APPLICATIONS OF RING OPENING OF CYCLOPROPYLCARBINYL RADICALS, AND SEQUENTIAL RADICAL RING CLOSURE–RADICAL RING OPENING FOR PREPARATION OF BENZOFURANS

I. INTRODUCTION

Radical ring closure has been investigated intensively[1] in the last few years and is now an important method in organic synthesis. However, the synthetic applications of the reverse process, i.e. radical ring opening, have not yet been widely appreciated. This situation is surprising because the physical organic chemistry of radical ring opening is a very well-studied area.

Most of the reported[2] measurements involve small rings because the opening of larger rings does not usually occur at an adequate rate,[2,#] unless substituents are present that stabilize the product radical. Extensive kinetic studies have been made for the parent system over a range of temperatures,[4,5a] and kinetic data are also available for cyclopropylcarbinyl systems carrying substituents such as methyl,[5] ethoxycarbonyl,[5b] and phenyl.[6]

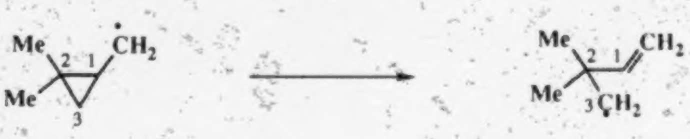
The parent system (Equation 1) has a rate constant for ring opening of $10^8\ \mathrm{s}^{-1}$ at 25 °C.[4,5] The reverse process is much slower, the rate constant being about $10^4\ \mathrm{s}^{-1}$. It should be noted that the absolute and relative values[4,5] of these rate constants can be influenced profoundly by the substitution pattern.



Eq. 1

[#] Fission of the C(9)-C(10) bond in the 9-decalinoxyl radical is fast but reversible (reference 3).

The substitution pattern also plays a role in the preferred regiochemistry of opening,[7] and the effects can be understood in terms of frontier molecular orbital theory. For example, in the reaction shown by Equation 2, the SOMO interacts preferentially with the LUMO of the C(1)-C(3) bond because the corresponding orbital of the C(1)-C(2) bond is raised in energy by the attached methyl groups, which are electron-releasing.



Eq. 2

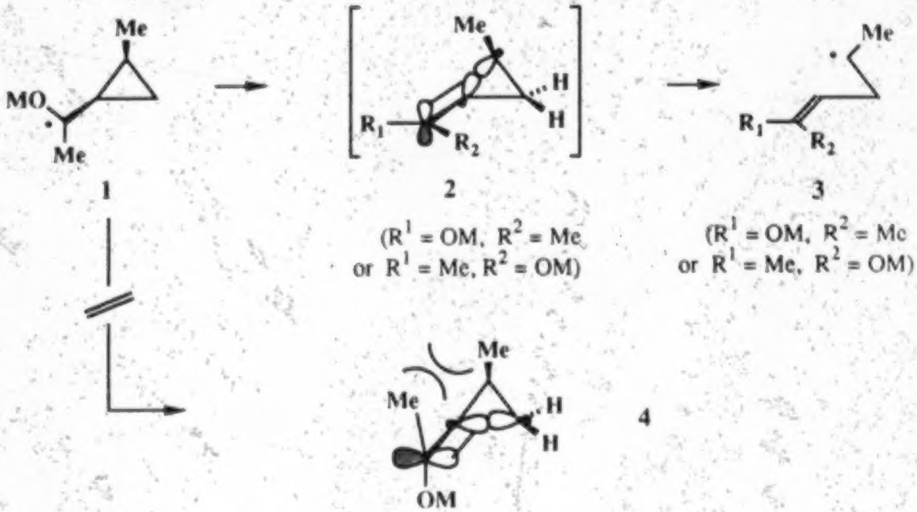
In disubstituted cyclopropanes, the relative geometry of the substituents can determine the regiochemistry of the radical ring opening because reaction will tend to take place through that conformation in which nonbonded interactions are minimized. Radical **1** (M = metal), for example, gives **3** (R^1 = OM, R^2 = Me or R^1 = Me, R^2 = OM) (Scheme 1). Clearly, conformation **2**, rather than **4** is involved in the process.[7b,8,#]

Some types of cyclopropylcarbinyl radical have been used in mechanistic studies[##] as radical clocks.

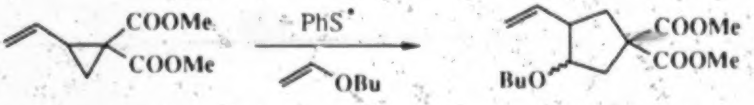
[#] The alternative to **4**, in which OM and attached Me are interchanged, is also disfavoured by non-bonded interactions.

[##] For a review on free radical clocks, see reference 9.

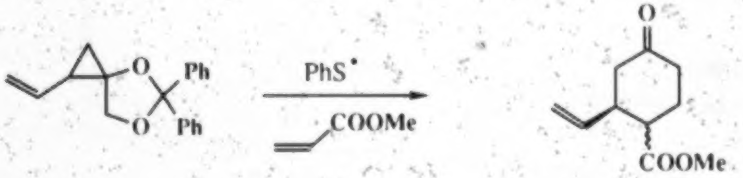
SCHEME 1


Me
MO
Me
1
Me
H
H
R1
R2
2
(R1 = OM, R2 = Me
or R1 = Me, R2 = OM)
Me
R1
R2
3
(R1 = OM, R2 = Me
or R1 = Me, R2 = OM)
Me
Me
H
H
OM
4

Recently, radical addition to vinylcyclopropanes has become an active area of research,[10] and typical applications are summarized in Equations 3[10b] and 4.[10i,11]

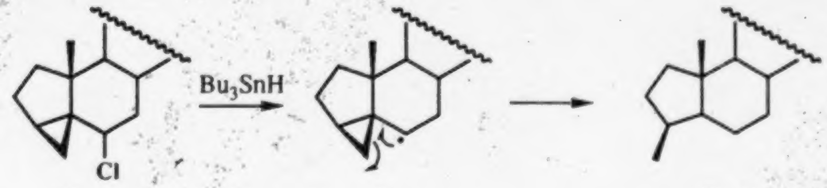

COOMe
COOMe
PhS•
OBu
COOMe
COOMe
BuO

Eq. 3

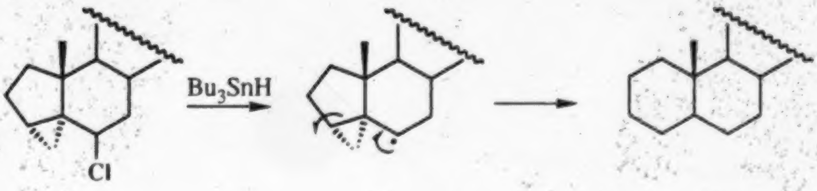

O
O
Ph
Ph
PhS•
COOMe
O
COOMe

Eq. 4

When the cyclopropane is fused to another cyclic structure stereoelectronic factors can be important in determining the regiochemistry of ring opening,[12,13,14] and the cyclopropyl bond that breaks is the one that overlaps best with the SOMO, as shown by Equations 5 and 6.

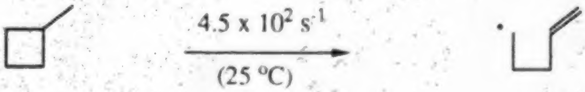


5a **5b** **5c** Eq. 5

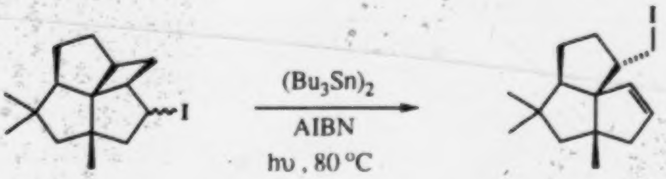


6a **6b** **6c** Eq. 6

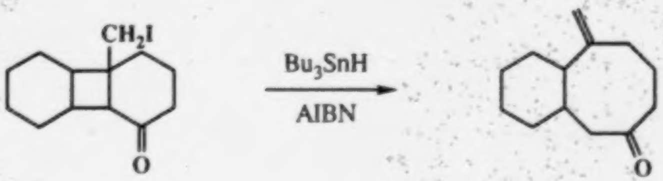
Although most physical chemical work has been done with three-membered rings, some rate measurements have been made for other ring sizes. Rate data are available for cyclobutylcarbinyl radicals (Equation 7),[2,15] and there is information on the regiochemistry[15a,16] and stereoelectronic features of the process. Very few synthetic applications are known; those we are aware of are summarized in Equations 8[17] and 9.[18]



Eq. 7

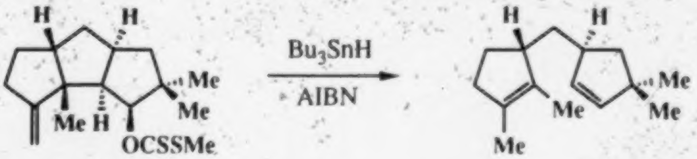

(Bu3Sn)2
AIBN
hυ, 80 °C
I

Eq. 8


CH2I
Bu3SnH
AIBN
O

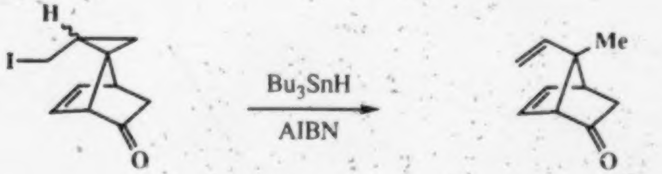
Eq. 9

Five-membered rings do open, but only if the resulting species is appropriately stabilized,[19,20] as shown in Equation 10.

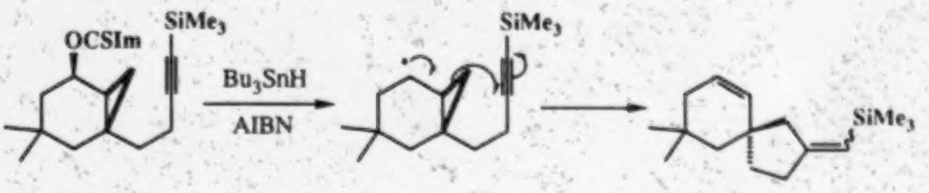

H
H
Me
Me
Me H
OCSSMe
Bu3SnH
AIBN
H
H
Me
Me
Me
Me

Eq. 10

The opening of cyclopropyl- and cyclobutyl-carbinyl radicals in which the ring is fused to a cyclic structure has very rarely been used in synthesis[17,21] (Equation 11), but the following work, and spirocyclizations of the type shown in Equation 12,[22] are the first attempts to develop the synthetic potential of such reactions.

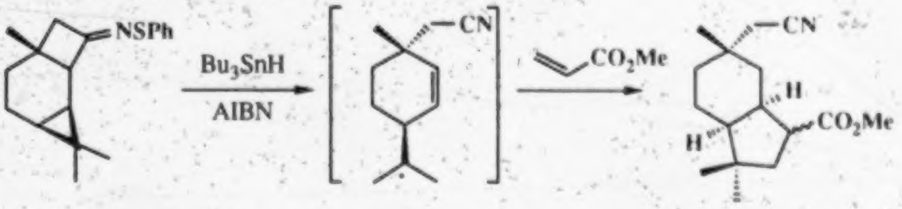

H
I
O
Bu3SnH
AIBN
Me
O

Eq. 11


OCSIm
SiMe₃
Bu₃SnH
AIBN
SiMe₃
SiMe₃

Eq. 12

Very recently, a further example has been reported (Equation 13).[23] It should also be mentioned that radical opening of epoxides[24,25] and aziridines[26] has been studied. These reactions appear to have some synthetic utility [25a,b,f,26] and the epoxide case is useful for detecting radicals.[27]


NSPh
Bu₃SnH
AIBN
CN
CO₂Me
CN
H
CO₂Me
H

Eq. 13

Finally, the opening of cyclopropylcarbinyl radicals is believed to be involved in a number of biochemical transformations.[28,#,##]

[#] Cyclopropylaminyl radicals may be involved in mechanism-based enzyme inhibition by cyclopropylamines: reference 29.

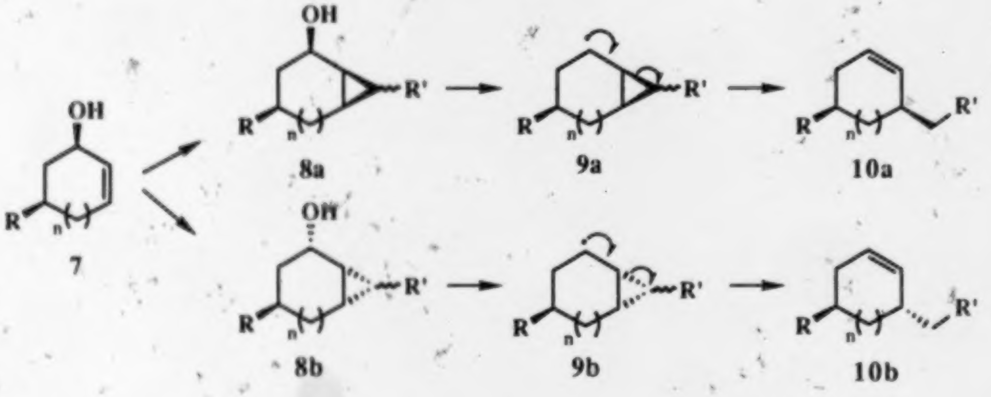
[##] Epoxides may be involved in the biosynthesis of Rifamycin S: reference 30.

II. RESULTS AND DISCUSSION[#]

(A) SYNTHETIC APPLICATIONS OF RADICAL RING OPENING

The sequence involved (Scheme 2) in the use of radical ring opening for the introduction of alkyl groups with stereocontrol, can be divided into three main stages. First, ways had to be selected to prepare the cyclopropanes and, preferably, the stereochemistry of the latter should be controlled (**7**→**8a** or **7**→**8b**). Second, an appropriate method had to be found that would allow introduction of a group adjacent to the cyclopropane that will serve as a radical precursor. Finally, it was necessary to determine what factors (i.e. experimentals conditions and/or substitution patterns) favor opening of the cyclopropane moiety in the desired sense to provide the alkyl substituted cycloalkenes (**9a**→**10a** or **9b**→**10b**).

SCHEME 2



[#] Some of these results have been published,[62b] some are in press[53,62a] and some have been submitted for publication.[44,62c]

1) Cyclopropanation

In this work, several cyclopropanation processes were used (Table 1, page 13-15). We first evaluated the classical Simmons-Smith reaction, as it can be done stereoselectively[31] using allylic alcohols. Indeed, there are many reports where treatment of cyclic allylic alcohols leads to formation of cyclopropyl alcohols in which both cyclopropane and hydroxyl group are syn to each other. The hydroxyl group present on the molecule also serves as a precursor to a radical.

We arbitrarely used the Zn/CH_2I_2/ultrasound system for the conversion of decalin alcohols **16a** and **17a** to **16b** and **17b**, respectively, and the $Zn(Cu)/CH_2I_2$ reagent for conversion of steroid **19b**→**19c** (Table 1). It will be noted that in cases where a readily accessible allylic alcohol does not have the desired stereochemistry, Mitsunobu inversion[32] can be used to make the necessary correction. The overall result is that both stereoisomeric cyclopropyl derivatives of an alkene precursor are accessible readily, as shown by preparation of decalin **17b** (stereoisomer of **16b**) and estrone derivative **19c** (stereoisomer of **18c**).

A very mild version of the Simmons-Smith reaction was reported recently in which zinc is replaced by samarium.[33] As this method was also suitable for making alkyl-substituted cyclopropane derivatives, we used it for the preparation of methylcyclopropane **20b** (45%, 69% based on conversion) by treatment of a cold (-78 °C) solution of **20a**# in THF with 1,1-diiodoethane and samarium amalgam, followed by slow warming to room temperature.

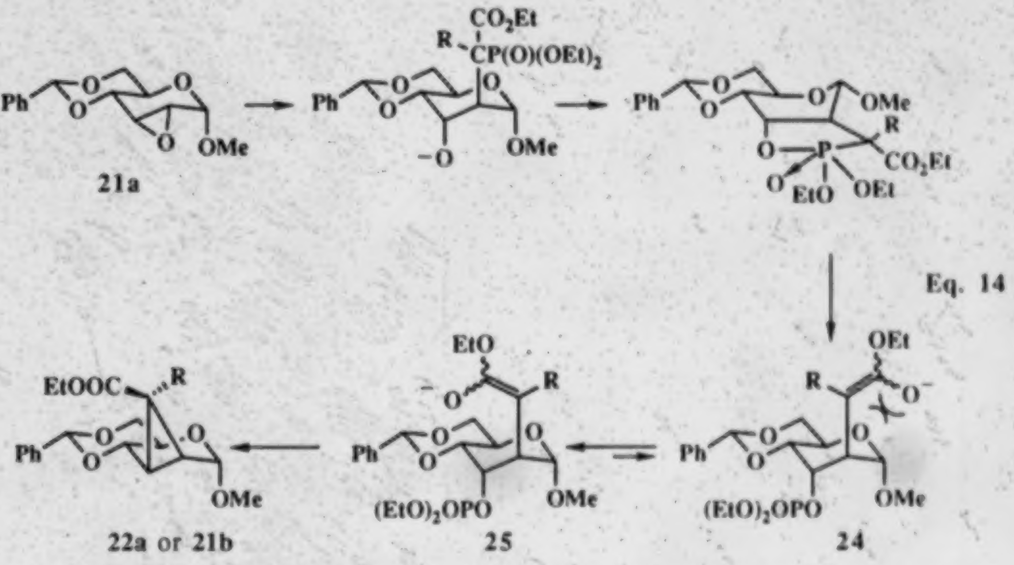
# Compound **20a** was prepared in four steps from 2-cyclopentene-1-acetic acid (see experimental).

Not unexpectedly, the nature of the samarium metal, i.e. the source and/or quality and/or mesh size, seemed to be of great significance, but we were eventually able to conduct the cyclopropanation cleanly and in reproducible yield.

Another means of generating cyclopropanes is by dichlorocarbene addition.[34] Compounds **14b** and **15b** were conveniently made in 71% and 73% yield, respectively, by treatment of a solution of **14a** or **15a** in chloroform with 50% w/w sodium hydroxide and a phase transfer catalyst. In both cases, yields were substantially higher when the reaction was stopped short of completion. The dichlorocarbene addition is reported to occur with stereochemical direction by the hydroxyl and the selectivity is thought to arise by hydrogen bonding of the alcohol to the active reagent. On this basis, the single product isolated in each case was assigned the stereochemistry indicated, where the cyclopropane is *syn* to the hydroxyl.

Corey *et al.*[35] reported an example where a three membered ring is generated by intramolecular carbene delivery and we applied this method to the preparation of **13d**. Acylation of cyclohexen-1-ol with a protected form of α-diazoacetyl chloride (TsNH-N=CHCOCl), followed by treatment *in situ* with triethylamine gave the desired α-diazoester **13b** in 70% yield. Slow addition of this material to a refluxing solution of a copper(II) catalyst in toluene gave the desired cyclopropane lactone **13c** (88%) with of course, complete stereocontrol. The latter was then converted (88%) to hydroxyamide **13d** using Me_2AlNMe_2.[36]

A different approach to a cyclopropane of predictable geometry, this time based on phosphonate chemistry, was used to construct the sugar derivatives **21b**[37] and **22a**.[38] In both cases, an epoxide of appropriate stereochemistry was available in a few trivial steps from an α-methyl glycoside. Sugar epoxide **21a** was treated with the ylid derived from triethyl 2-phosphonopropionate. The ylid attacks at C-2 to give a pentacoordinate species as an intermediate[39](Equation 14). This species collapses to afford conformers **24** and **25**. In **24**, the interaction between the electrons on the ring oxygen and those in the π cloud of the enolate ion is disfavored vis a vis **25**. Ring closure from the latter then leads to the desired cyclopropane derivative as a single isomer.



Eq. 14

It is reported[38] that in the case of **21a** many efforts were made to convert it into cyclopropane **22a** under a wide variety of conditions. However, with all the solvents and temperatures tried, the reaction proceeded in poor yield (1 to 17%) unless it was conducted in dioxane at 160 °C in a special stainless steel pressure vessel.[38] Those conditions were most inconvenient for a multigram reaction, and therefore, we sought of an alternative whereby dioxane (an ethereal solvent) would be replaced by a solvent of similar nature but with a boiling point high enough that the use of a pressure vessel could be avoided. When the reaction was conducted on a 20g scale in triglyme at 140 °C, **22a** was obtained in 45% yield. This result compares favorably with the yield reported (45%) in the literature, and requiring the use of a pressure vessel.

Enones can also serve as substrates for direct cyclopropanation. Conversion of cyclohexenone **11a** or the estrone derivative **12a**[#] to the cyclopropane esters **11b** and **12b** was achieved using sulfur ylide chemistry ($Me_2S{=}CHCO_2Et$).[41] The reaction proceeds by conjugate addition of the reagent to the enone to produce an enolate which displaces the Me_2S^+ group intramolecularly to give a cyclopropane bearing a carboethoxy substituent. The non-substituted version of **12b**, i.e. **18b**, was obtained very similarly using $CH_2{=}S(O)(CH_3)_2$. In all three examples, the ketone was then reduced to the corresponding alcohol **11c**, **12c**, and **18c**, in order to provide the group that will serve eventually as the radical precursor. Of course, the procedure based on enones cannot be adjusted at will to place the cyclopropane on either face of the molecule.[42]

Clearly, a wide variety of cyclopropanation conditions are available and therefore it is likely that one can be found that is compatible with functional groups present in a given molecule and allows the cyclopropanation to be

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[#] Compound **12a** was synthesized in five steps from commercially available estrone, following a literature procedure.[40]

TABLE 1[a]

Preparation of cyclopropane derivatives

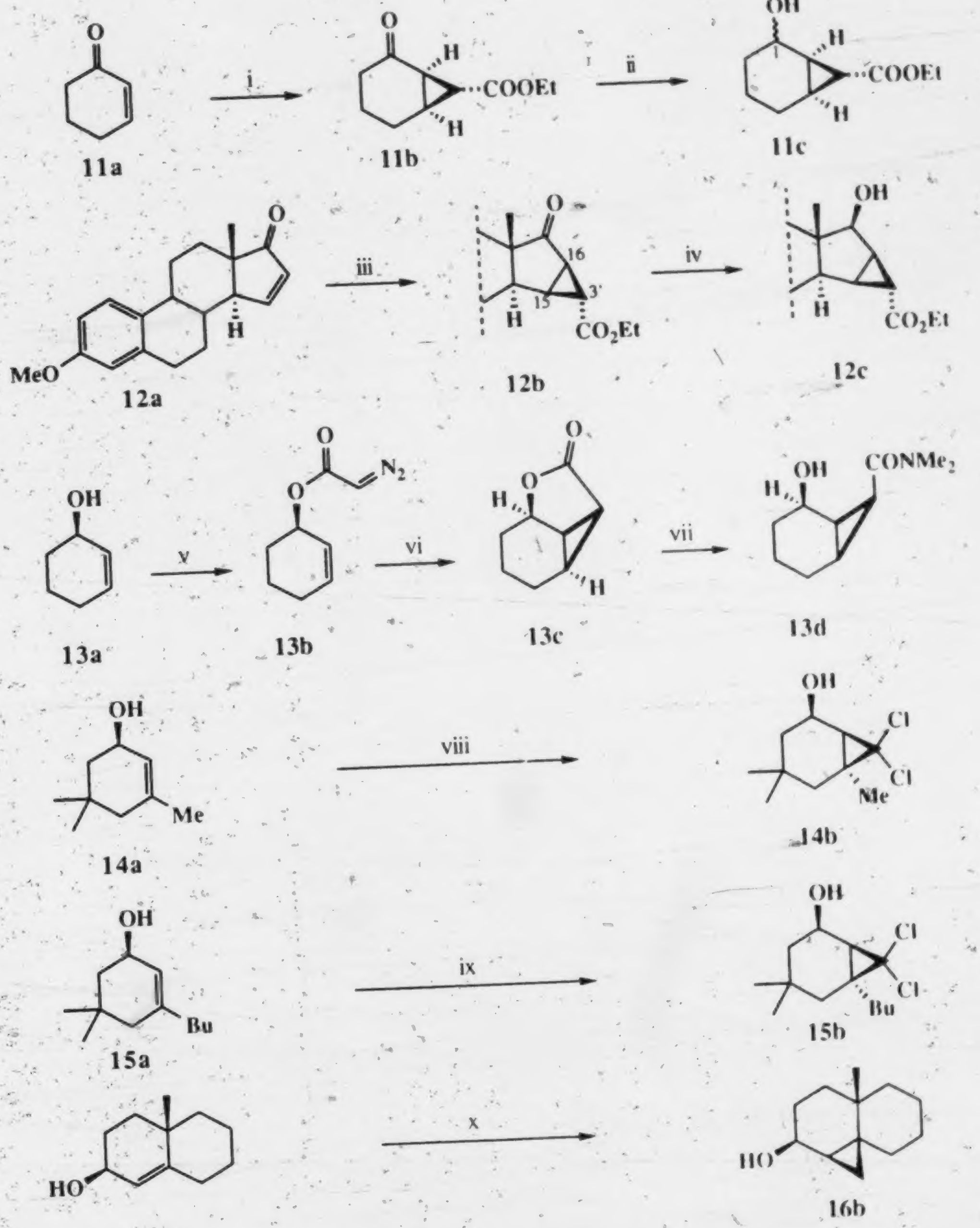
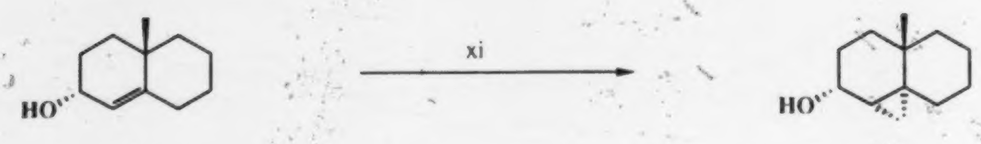
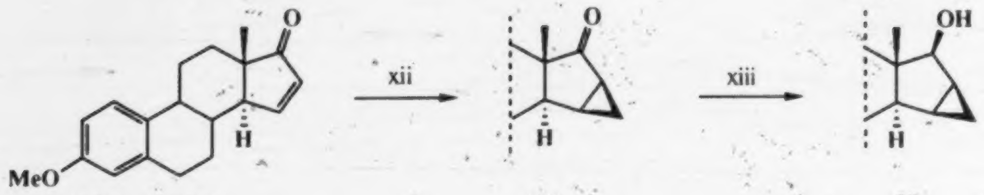

11a
i
11b
COOEt
ii
11c
OH
COOEt
12a
MeO
iii
12b
16
15
3'
CO$_2$Et
iv
12c
CO$_2$Et
13a
v
13b
N$_2$
vi
13c
vii
13d
CONMe$_2$
14a
Me
viii
14b
Cl
Cl
Me
15a
Bu
ix
15b
Cl
Cl
Bu
16a
HO
x
16b
HO

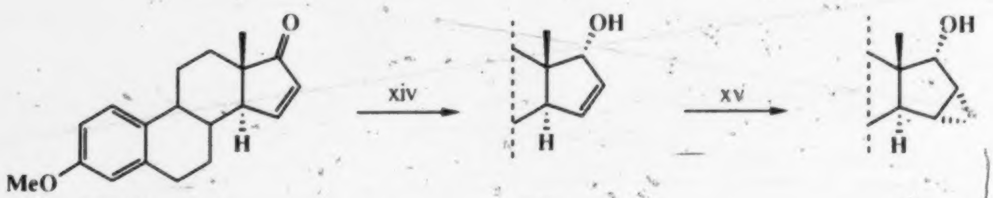
TABLE 1 Cont'd



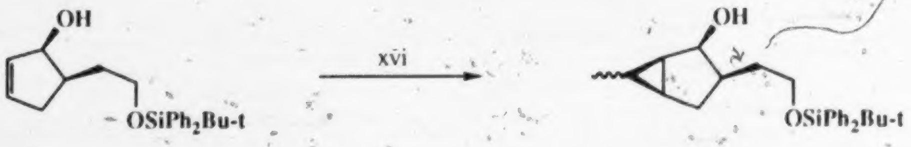
17a 17b


O
MeO
H
xii
O
H
xiii
OH
H

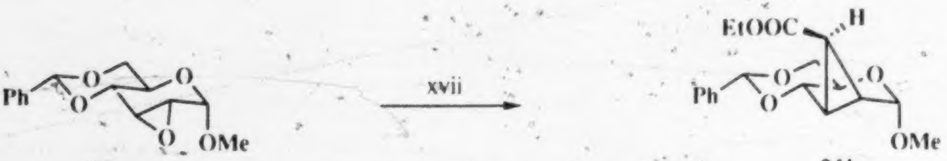
18a (= 12a) 18b 18c


O
MeO
H
xiv
OH
H
xv
OH
H

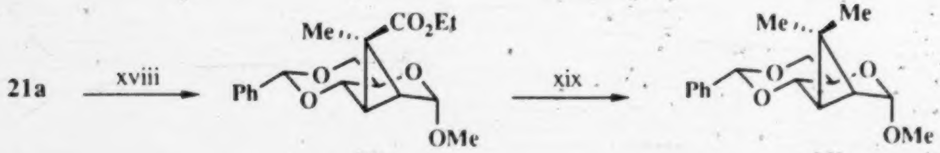
19a (= 12a) 19b 19c


OH
OSiPh$_2$Bu-t
xvi
OH
OSiPh$_2$Bu-t

20a 20b


Ph
O
O
O
O
OMe
xvii
EtOOC
H
Ph
O
O
O
OMe

21a 21b


21a
xviii
Me
CO$_2$Et
Ph
O
O
O
OMe
xix
Me
Me
Ph
O
O
O
OMe

22a 22b

Footnotes to Table 1. (i) $Me_2S{=}CHCOOEt$; 73%. (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH; 85%. (iii) as in (i). (iv) as in (ii). (v) $PhNMe_2$, $TsNHN{=}CHCOCl$, then Et_3N; 70%. (vi) bis-(*N*-*t*-butylsalicylaldiminato)copper(II); 88%. (vii) Me_2AlNMe_2; 93%. (viii) Aq NaOH, $PhCH_2N^+Et_3Cl^-$, $CHCl_3$; 71%. (ix) as in (viii); 73%. (x) CH_2I_2, Zn, DME, sonication; 68%. (xi) as in (x); 82%. (xii) $Me_3S^+(O)I^-$, NaH, DMSO; 72%. (xiii) $LiAlH_4$; 89%. (xiv) as in (ii); Ph_3P, $EtOOC{-}N{=}N{-}COOEt$, PhCOOH; aq NaOH (5 M); 65% from **19a**. (xv) CH_2I_2, Zn(Cu); 81%. (xvi) CH_3CHI_2, Sm, $HgCl_2$; 45%. (xvii) $EtOOCCH_2P(O)(OEt)_2$, NaH; 46%. (xviii) $EtOOCCH(Me)P(O)(OEt)_2$, NaH; 45%. (xix) see ref. 38.

[a] Where stereochemical assignments are tentative, this fact is indicated in the experimental section.

effected with stereocontrol. Mitsunobu inversion allows access to both isomeric alcohols and therefore to both isomeric cyclopropane derivatives. Moreover, assymetric cyclopropanation[42] is also available for construction of molecules in optically pure form, but we did not examine this possibility.

2) Introduction of the radical precursor

The second stage of the process shown in Scheme 2 involves introduction of the radical precursor. In most case, this was achieved by converting the alcohol to a phenylseleno derivative (Table 2, page 27-29).

At first we used the standard method[43] whereby tributylphosphine is added to a solution of the alcohol and phenylselenocyanate in THF. However this method was not satisfactory as the reactions would often not go to completion. The use of a large excess of both reagents made no significant difference. We eventually found that by slowly adding a solution of phenylselenocyanate in THF to a solution of the substrate and tributylphosphine in the same solvent, very significant improvements were achieved, and we now prefer this procedure. In other cases, we have found that replacement of the hydroxyl by the selenium unit did not always involve clean inversion of stereochemistry, but this is of no consequence since both epimers at the selenium-bearing carbon afford the same radical.

Although the conversion of a hydroxyl to a selenide works very nicely, purification of the latter by flash chromatography is necessary to remove the phosphine byproducts and this is not suitable for a large scale work. Conversion on a multigram scale of **14b** to **14c**, was achieved therefore by a more convenient two step procedure.[#]

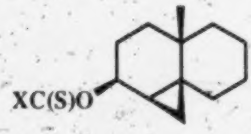
Alcohol **14c** was cleanly converted (80-90%) to the corresponding tosylate as a white crystalline compound which can be recrystallised easily. The tosylate can be kept for months in the refrigerator, but if it is left standing on the bench for a day or two, it decomposes to a black tar. Nucleophilic displacement of the tosylate with 1.05 equiv of PhSeNa in THF-HMPA[45] afforded the desired selenide **14c** in 91% yield after simple filtration through a short pad of silica to remove polar material.

A problem often encountered in the preparation of selenides is the necessity of removing diphenyl diselenide which invariably forms during the process. This problem can sometimes be serious if the selenide is non-polar and co-runs with diphenyldiselenide on silica gel. Purification is then very difficult if not impossible. This problem was encountered on many occasions during the course of this project, but we have been able to find a general solution.

[#] The conversion of **14a** to **14d** has been submitted for publication, see reference 44.

Treatment of the crude material with sodium borohydride (see experimental) converts diphenyldiselenide to PhSeNa without affecting the selenide to be purified. Once the yellow coloration characteristic of diphenyl diselenide has disappeared, the solution is treated with bromoacetic acid which converts the $PhSe^-$ anion to (phenylseleno)acetic acid; the latter is conveniently removed from the selenide by extraction into aqueous base.

An obvious alternative to selenides as radical precursors is the use of thiocarbonyl derivatives. However, because the selenides could be prepared easily and the selenide unit served its role of radical source very well,[46] (see later) we did not examine the alternative thiocarbonyl thoroughly. In the few examples we tested, i.e. **26-28**[#] we found that the traditional thermal deoxygenation[48] in refluxing benzene[##] was unsuitable, but we did not try reaction at a low temperature using the triethylborane method.[50]



26 X = Imidazolyl
27 X = OPh
28 X = SMe

[#] With the standard preparations given in reference 47 and 48, the yields of **26**, **27**, and **28** were 76%, 75%, and 45% respectively.

[##] One of the problems, we encountered was extensive formation of olefinic material, tentatively assigned as structure **29** (see page 20). However, for a very successful related use of the classical Barton deoxygenation, carried out in refluxing benzene, see reference 50.

The carbohydrate examples were dealt with differently and neither selenides nor thiocarbonyl groups were used as the radical precursor. Close inspection of sugar **21b** (=**23b**) revealed that it could be elaborated into derivatives in which a radical precursor could be placed either on the right or on the left of the cyclopropane moiety. In principle, therefore, opening of the cyclopropane could be achieved from either side.

The diol moiety of **23b** (=**21b**) was released (H_2 / Pd/C) and protected as the diacetate (acetic anhydride, pyridine). Then, acetolysis of the methyl glycoside followed by treatment of the resulting anomeric acetate with bromotrimethylsilane[51] gave the required anomeric bromides **23c** in good overall yield (> 74%). (hydrogen bromide in acetic acid was unsatisfactory in this case.) From this radical precursor, the possibility of opening the righthand side of the cyclopropane moiety arises. On the other hand, treatment of the same material (i.e. **21b**) with NBS in carbon tetrachloride led to the bromobenzoate derivative **21c**, in which the benzoate unit will serve as the radical precursor. This process allows the possibility of opening the lefthand side of the cyclopropane moiety.

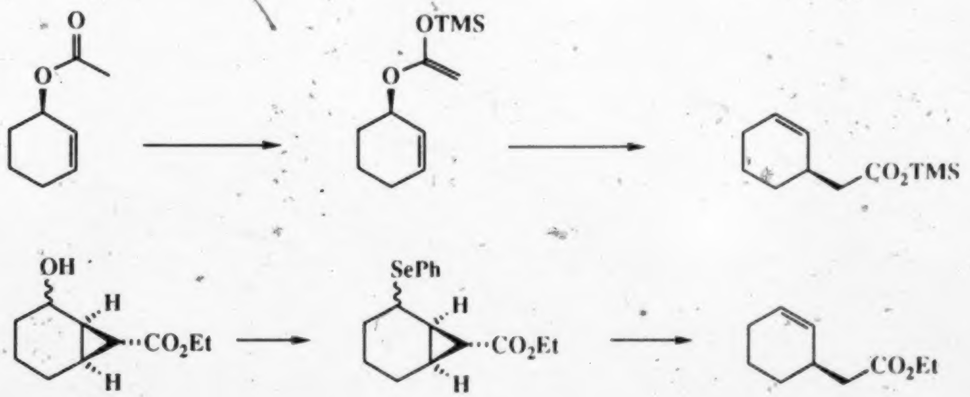
Finally, the dimethyl analog **22b**,# which is readily accessible from **22a**, was also converted (71%) to the bromo benzoate **22c** using NBS in carbon tetrachloride.[52]

# Prepared from **22a** according to the literature procedure.[38]

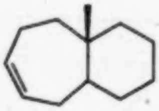
3) Generation of the radical and ring opening

The third stage of the process shown in Scheme 2 involves generation of a radical at the carbon bearing the hydroxyl. The conditions used for generating the radical and opening of the ring were determined by the nature of the radical precursor and by the substituents on the cyclopropane moiety. In most cases, where a strong electron-withdrawing group is present (i.e. CO_2Et in the case of **11d**, **12d**, and **23c** or $CONR_2$ in the case of **13e**), addition of stannane and initiator (each in one portion) to a solution of the substrate in refluxing benzene, was employed successfully. In no case did we observe formation of products resulting from ring expansion or from simple reduction without ring opening. It will be noted that the process represents in these examples a radical equivalent of an Ireland ester-enolate rearrangement (Scheme 3).

SCHEME 3



In contrast, studies with unsubstituted cyclopropanes like decalin **16c** showed significant amounts of ring expansion product under these conditions. Indeed, when radical ring opening of **16c** was conducted in refluxing benzene, the ^1H NMR spectrum of the product mixture showed a doublet of triplets at δ 5.28 and 5.51. The signals correspond to the two vinylic hydrogens of **16d**, which is a known compound. However, the material was contaminated with *ca* 55 mol% of an olefinic side product tentatively identified as **29** on the basis of the high multiplicity of the vinylic hydrogens which resonate at δ 5.55--5.72. Repeating the reaction at higher temperature, and/or adding the stannane and/or substrate slowly did not result in any improvement.



29

The fact that ring expansion is a competing process here is not surprising as the decalin system **16c** has a feature which represents a very unfavorable case. Not only is the cyclopropane moiety unsubstituted which, as we will see later, makes ring expansion more favorable, but the desired process leads to a primary radical as an intermediate whereas ring expansion (internal homolysis) generates the much more stable tertiary radical. In most cases competition will be between primary and secondary radicals for peripheral and internal homolysis, respectively and, therefore, inhibition of ring expansion should be easier.

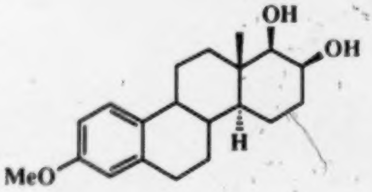
It was eventually found that, by conducting the reaction at lower temperatures (0 °C), an 84% yield of the desired product **16d**, contaminated by less than 5% of ring expansion product **29**, could be obtained. From now on all the reactions involving substrates containing a cyclopropane lacking an electron withdrawing substituent were conducted at low or moderate temperatures (-20 °C to 25 °C). The procedure consists simply of irradiating a cooled solution of the substrate and stannane with a domestic sunlamp.

Estrone derivatives **18d** and **19d** were also treated with stannane at low temperature, and under these conditions a good yield (72%) of the desired methyl substituted cyclopentene derivatives **18e** and **19e**, respectively, were obtained along with some (*ca* 14%) ring expansion product **18f** **(=19f)**. These two examples clearly show that, by using the same starting material, the methodology allows formation of a cyclopropane on either face of the molecule and, after radical ring opening, leads to isomers whose newly introduced substituents are on opposite faces.

It is appropriate at this point to comment on the ring expansion product **18f**. The latter had to be unambiguously identified by comparison with an authentic sample. It was decided that the effort spent in preparation of an authentic sample, would serve at the same time to study the properties of a novel titanium reagent that was being developed in our laboratories.[53] The reagent, which is made from C_8K (2 moles) and titanium trichloride (1 mole), had been successfully used for the coupling of sensitive dicarbonyl compounds to give olefins[53] (McMurry coupling), and we wanted to test the feasibility of the process whereby a diol would be converted to an olefin.

We felt that this process should work since a diol derivative is quite likely formed as an intermediate in the dicarbonyl coupling.

Therefore, the precursor of olefin **18f** would be the diol **30** and the latter is readily accessible in four steps from methyl estrone.[54] We were pleased to find that treatment of diol **30** with C_8K and titanium trichloride in refluxing diglyme gave a 92% yield of the expected olefin **18f**, and that its ^1H NMR and ^{13}C NMR were identical to those of the olefinic byproduct obtained in the radical ring opening sequence. Hence the structure assigned to **18f** was confirmed.



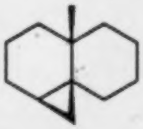
30

Whereas ring expansion competes to a certain extent in the case of unsubstituted cyclopropane derivatives, the presence of a methyl substituent on the cyclopropane moiety seems to suppress the formation of ring expansion products, as shown with selenide **20c**. Treatment of the latter with stannane at a moderate temperature (25 °C) gave the desired ethyl cyclopentene product **20d** (65%) with no evidence of a ring expansion product.#

# Compound **20d** was slightly contaminated with 4% of unidentified byproduct.

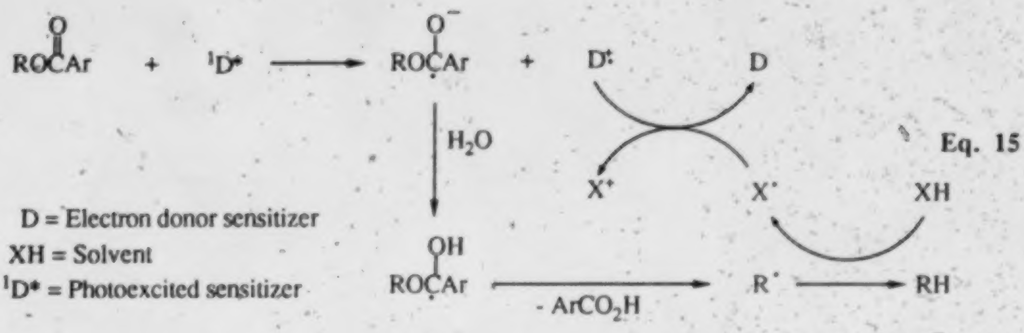
In the case of selenide **14c**, where two chlorine substituents are present on the cyclopropane, the reaction was also conducted at low temperature (-10 °C) and the desired dichloromethyl cyclohexene **14d** was obtained in excellent yield (> 90%). Maintenance of a low temperature in this case also serves to inhibit dechlorination. With the analog **15c**, we deliberatly reduced the initial ring-opened product further so as to obtain the monochloride **15d** (92%).

Although in most cases we have used triphenyltin hydride, we found it was sometimes preferable to use the tributyl analog. In some examples separation of the tin byproducts is easier with one or the other of the stannanes. In the case of decalin **16c**, the optimum conditions called for use of tributyltin hydride. This is a poorer hydrogen donor[55] and its use served to inhibit more efficiently the formation of cyclopropane **31**.



31

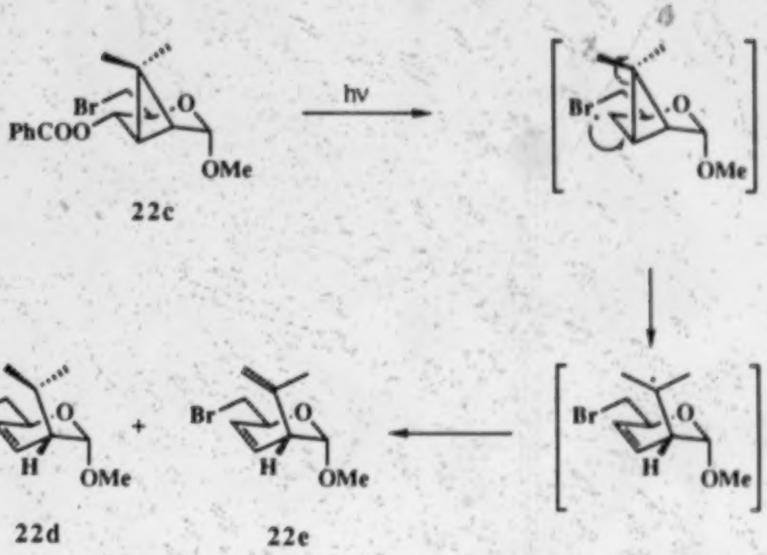
All the conditions developed to generate the radicals, were suitable for use with selenides. In the case of the carbohydrates **21c** and **22c**, the radical precursor is a benzoate and therefore a photochemical method was used.[56] The method consists of irradiating a solution of the substrate, *N*-methylcarbazole and magnesium perchlorate in THF-water with a high pressure mercury lamp. Under these conditions, a radical is generated at the carbon bearing the benzoate, and the ring-opening process takes place as with the previous examples. The mechanism of the photochemical process is shown in Equation 15.


ROCAr
^{1}D*
ROCAr
D$^{+\cdot}$
D
H$_2$O
X$^+$
X$^\cdot$
XH
D = Electron donor sensitizer
XH = Solvent
^{1}D* = Photoexcited sensitizer
OH
ROCAr
- ArCO$_2$H
R$^\cdot$
RH

Eq. 15

Using **21c** as the starting material the desired ring-opened product **21d** was obtained in excellent yield (86%). It should be noted that this conversion, combined with the previously discussed conversion of anomeric bromides **23c** to **23d**, serves to illustrate the fact that it is possible to prepare a carbohydrate cyclopropane flanked on either side by a potential radical precursor. Hence regiochemical control is possible, and the substituents resulting from cyclopropane opening can be placed at one or other of two sites.

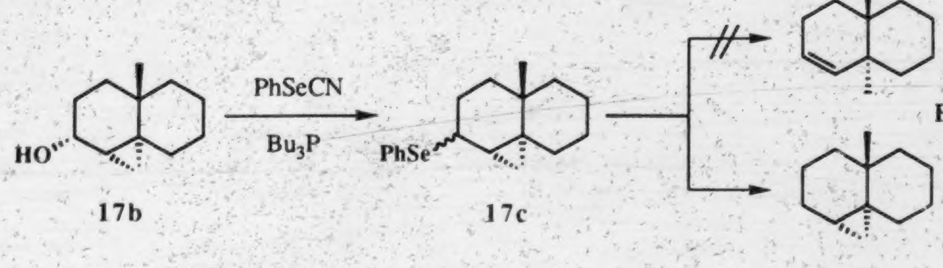
With the corresponding dimethyl cyclopropane analog **22c**, the expected products **22d** and **22e** (1:1 ratio) were obtained in 67% yield. The fact that two products arise has nothing to do with the ring opening process itself but is simply due to the fact that during the process, a tertiary radical is formed. Under the photochemical conditions used, tertiary radicals readily disproportionate[56] to give, in this case, isopropyl and isopropenyl derivatives **22d** and **22e**. (Equation 16).



Eq. 16

It should be noted with this last example that no ring expansion is observed even though no strong electron-withdrawing substituent is present on the cyclopropane. This outcome was expected since the temperature of the reaction mixture was low enough (room temperature) to inhibit the competing processes. Moreover, in contrast to the procedure based on stannane chemistry, the photochemical method is compatible with the presence of a bromine atom. Indeed, in the transformations we have just discussed, i.e. **21c**→**21d**, and **22c**→(**22d** + **22e**), the bromine atom that was present was left untouched.

Compound **17c** was the only example we found that did not undergo ring opening (see experimental) under our standard conditions, but gave instead **32** as the major (> 80%mol) compound (Equation 17). We attribute[57] this to the fact that the conformation of the molecule results in poor overlap between the radical center and all the cyclopropane carbon-carbon bonds.



Eq. 17

Finally, before concluding our studies on cyclopropane ring opening, we decided to repeat reactions that were originally achieved by photochemical initiation (sunlamp) by using a newly introduced method[50] which consists of treating a solution of the substrate and stannane at room temperature with triethylborane and a controlled amount of air. The role of triethylborane is to serve as a radical initiator by the mechanism depicted in Equation 18.

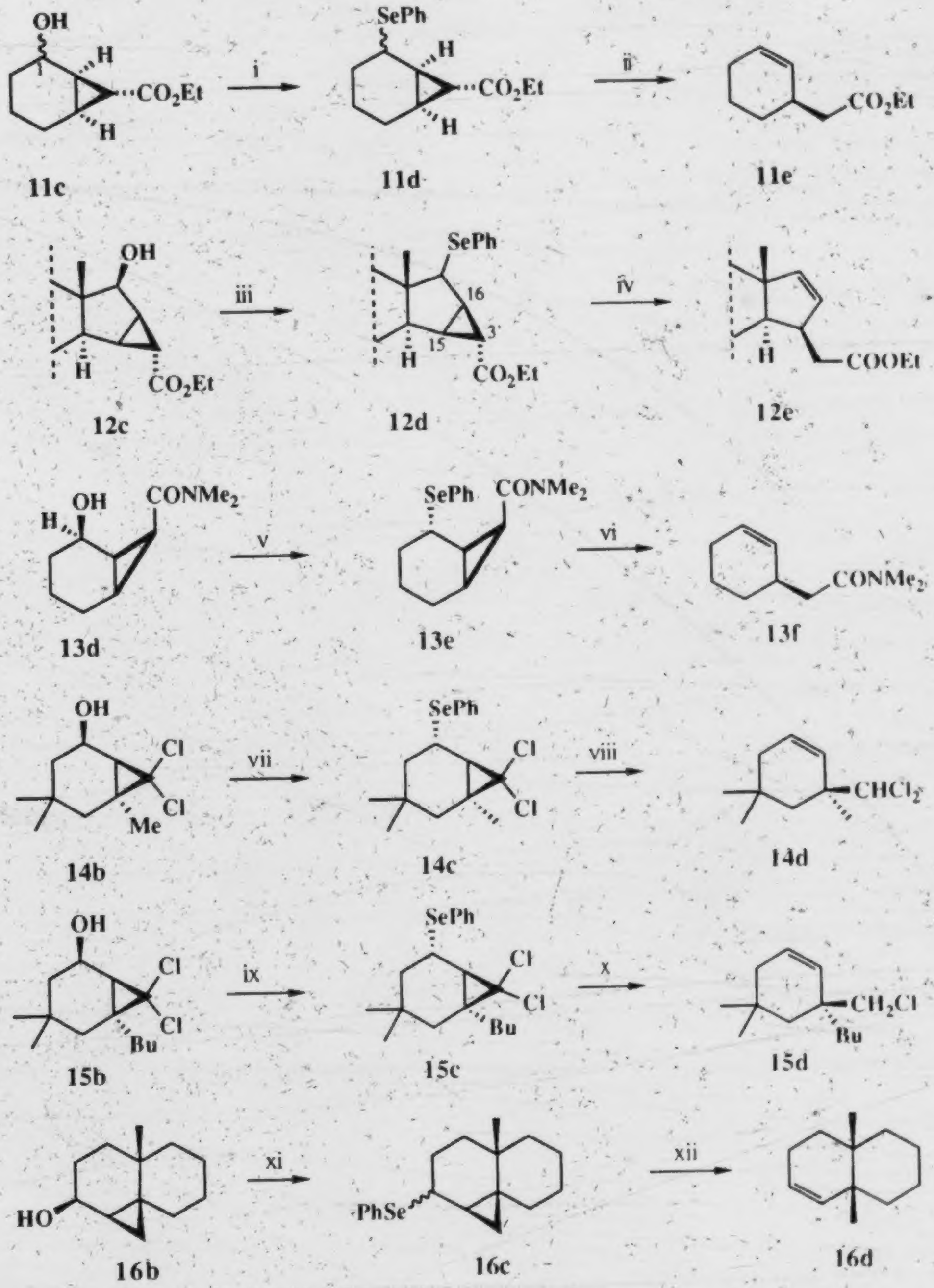
$$Et_3B \xrightarrow[O_2]{} \left[Et_3BO_2\right] \longrightarrow Et_2B{-}O{-}O\cdot + Et\cdot \xrightarrow[R_3SnH]{} R_3Sn\cdot + EtH$$

Eq. 18

In the three cases we examined, i.e with the dichloro derivatives **14c** and **15c** and with the decalin **16c**, the reaction performed under these new conditions worked very well (see experimental) and so this method represents a convenient alternative to photochemical initiation.

TABLE 2[a]

Introduction of the radical precursor and ring opening step


OH
H
CO2Et
H
1
i
SePh
H
CO2Et
H
ii
CO2Et
OH
CO2Et
H
iii
SePh
16
3'
15
H
CO2Et
iv
H
COOEt
H
OH
CONMe2
v
SePh
CONMe2
vi
CONMe2
OH
Cl
Cl
Me
vii
SePh
Cl
Cl
viii
CHCl2
OH
Cl
Cl
Bu
ix
SePh
Cl
Cl
Bu
x
CH2Cl
Bu
HO
xi
PhSe
xii

11c 11d 11e

12c 12d 12e

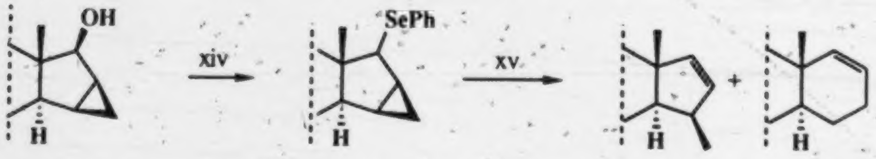
13d 13e 13f

14b 14c 14d

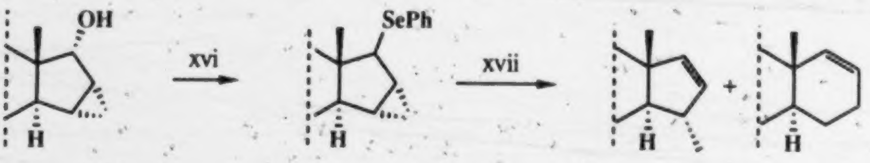
15b 15c 15d

16b 16c 16d

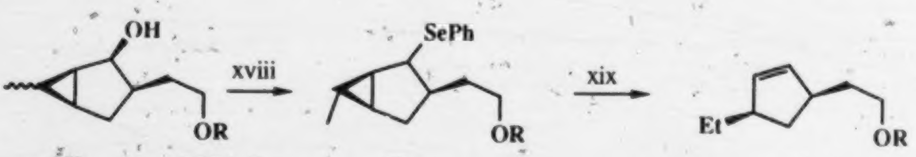
TABLE 2 Cont'd


OH
xiv
SePh
xv
+
H
H
H
H

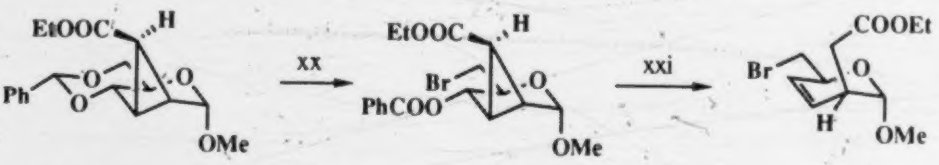
18c **18d** **18e** **18f**


OH
xvi
SePh
xvii
+
H
H
H
H

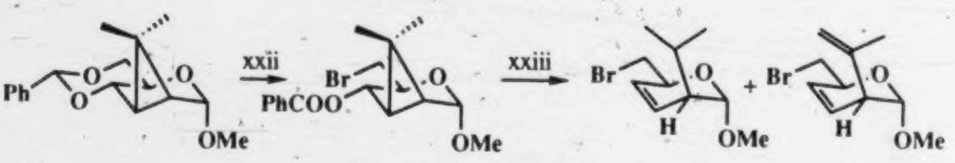
19c **19d** **19e** **19f (= 18f)**


OH
OR
xviii
SePh
OR
xix
Et
OR

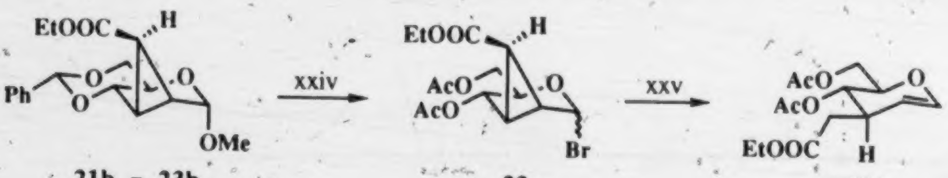
20b R = $OSiPh_2Bu$-t **20c** **20d**


EtOOC
H
Ph
O
O
O
OMe
xx
EtOOC
H
Br
PhCOO
O
OMe
xxi
COOEt
Br
O
H
OMe

21b **21c** **21d**


Ph
O
O
O
OMe
xxii
Br
PhCOO
O
OMe
xxiii
Br
O
H
OMe
+
Br
O
H
OMe

22b **22c** **22d** **22e**


EtOOC
H
Ph
O
O
O
OMe
xxiv
EtOOC
H
AcO
AcO
O
Br
xxv
AcO
AcO
O
EtOOC
H

21b = 23b **23c** **23d**

Footnotes to Table 2. (i) Bu_3P, PhSeCN; 80%. (ii) Ph_3SnH, AIBN; 92%. (iii) as in (i); 59% from **12a**. (iv) Bu_3SnH, AIBN; 90%. (v) as in (i); 78%. (vi) as in (ii); 96%. (vii) as in (i); 82%; or *p*-toluenesulfonyl chloride, DMAP, pyridine; then PhSeNa, HMPA; 81% from **14b**. (viii) Ph_3SnH, sunlamp; 96%; or Ph_3SnH, Et_3B; 92%. (ix) as in (i); 92%. (x) Ph_3SnH, Et_3B; 96%. (xi) as in (i); 82%. (xii) Bu_3SnH, sunlamp; 84% [containing some impurities (7%)]; or Bu_3SnH, Et_3B; 85% [containing some impurities (3%)]. (xiv) as in (i); 80%. (xv) Bu_3SnH, sunlamp; **18e**:**18f**::84:16; 94%. (xvi) as in (i); 63%. (xvii) as in (xv); **19e**:**19f**::84:16; 86%. (xviii) as in (i); 58%. (xix) as in (xv); 69%. (xx) NBS, $BaCO_3$; 82%. (xxi) *N*-methylcarbazole, $MgClO_4.6H_2O$, hv; 86%. (xxii) as in (xx); 71%. (xxiii) as in (xxi); **22d**:**22e**::1:1; 67%. (xxiv) H_2, Pd-C; Ac_2O, pyridine; Ac_2O, H_2SO_4 (catalytic); Me_3SiBr; >74% overall. (xxv) as in (iv); >80%. [a]Where stereochemical assignments are tentative, this fact is indicated in the experimental section.

4) Conclusion

The above results show that radical ring opening of cyclopropane carbinols is a general method for attaching alkyl and substituted alkyl groups to an existing cyclic structure and it can often be carried out with predictable stereo- and regiochemical control. Where the non-bridgehead carbon of the cyclopropane carries a strongly electron-withdrawing group the ring opening can be done at the reflux temperature of benzene and proceeds efficiently. However, in the absence of such electron-withdrawing groups a low temperature is best used in order to suppress ring expansion.# Like many radical-based methods the procedure is compatible with a range of functionality and the required radicals can be generated by a number of different and complementary methods.

#But *cf.* reference 22

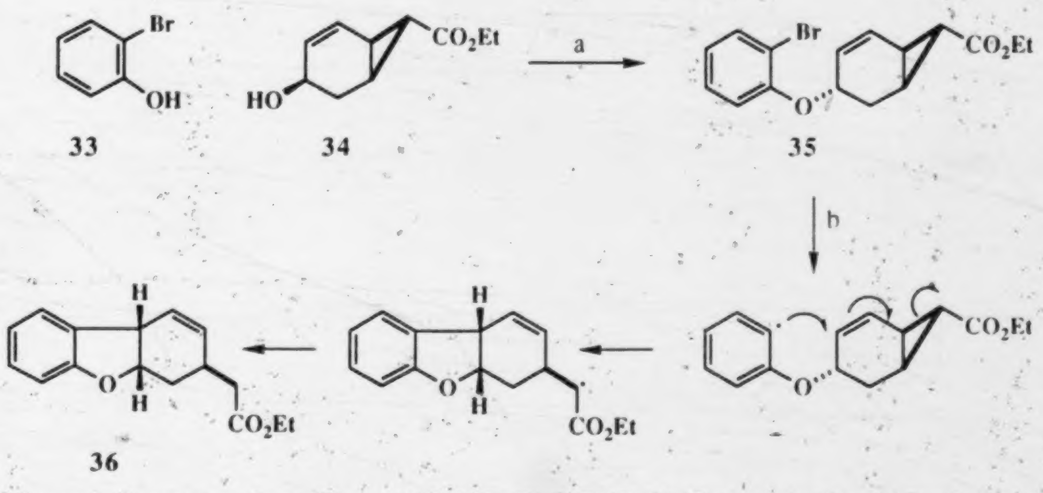
(B) SEQUENTIAL RADICAL RING CLOSURE--RADICAL RING OPENING: USE IN THE PREPARATION OF BENZOFURANS

Encouraged by the above results, we decided to combine the methodology with conventional radical ring closure in such a way that benzofuran derivatives would be readily accessible. The ultimate goal was not necessarily to provide a new route to benzofurans, but rather to evaluate the feasibility of the radical closure-ring opening process on a system which, at the same time, would give access to compounds we were interested in at the time (for evaluation as inhibitors of leukotriene biosynthesis).[58]

1) Preparation of benzofurans

The radical closure-ring opening sequence, involves Mitsunobu coupling of *o*-bromo phenol **33** with the functionalized alcohol **34** (Scheme 4).

SCHEME 4

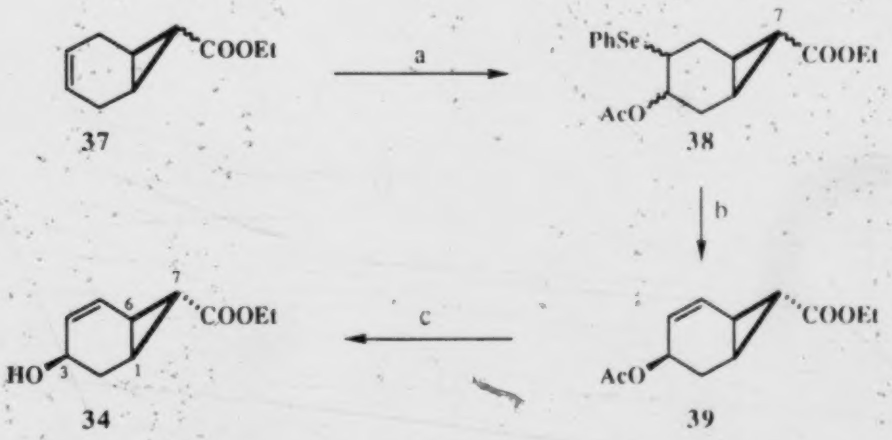


Scheme 4. Reagents and conditions: (a) DEAD, Ph_3P, THF, -20 °C to rt, 1 h, 33%; (b) Bu_3SnH, Et_3B, hexane, 35 °C, 24 h, 67%.

Treatment of the coupled product **35** with stannane would generate an aryl radical which should undergo a very facile 5-exo ring closure to give an intermediate in which the newly formed radical is adjacent to the cyclopropane moiety. Therefore, ring opening should take place and, after reduction of the ring-opened radical intermediate by stannane, the tricyclic product **36** would be obtained.

The required alcohol **34** was synthesized as follows (Scheme 5). Conversion of the known olefin **37**[59] to the corresponding epoxide using a wide variety of epoxidizing agents (*m*-chloroperbenzoic acid, Davis's reagent, hydrogen peroxide in benzonitrile) proceeded with little stereoselectivity[60] and it was therefore desirable to devise a better route. A variety of selenenylation conditions were then attempted, and it was eventually found that treatment of the same olefin **37** with benzeneselenenyl bromide and potassium acetate,[61] provided much greater facial discrimination. Indeed, this procedure afforded the selenoacetates **38** in 65% yield after purification.

SCHEME 5



Scheme 5. Reagents and conditions: (a) PhSeBr, AcOK, AcOH, 2 h, *ca* 65%; (b) 30% aqueous H_2O_2, pyridine, THF-CH_2Cl_2, 2 h, *ca* 93%; (c) EtONa, EtOH, 2 h, 79%.

The major component [AcO and C(7) syn] constituted 85 mol% of the mixture (^{1}H NMR). Oxidation of selenides **38** with hydrogen peroxide was followed by selenoxide elimination to afford the allylic acetate **39**. This was largely [>85 mol% (^{1}H NMR)] one isomer. Deacetylation (sodium ethoxide) and purification of the crude material gave the desired alcohol **34** (ν_{max} 3450, 1720 cm^{-1}) as a single isomer. The ^{1}H NMR spectrum showed two sets of olefinic signals at δ 6.25 (dd, J = 9.8, 3.8 Hz) and δ 5.75 (dd, 9.8, 5.2 Hz). The carbinyl hydrogen resonated in the expected region [i.e., δ 4.3 (m)] and the signals corresponding to the hydrogens on the cyclopropane ring all overlapped in the δ 1.8 to 2.1 region.

In order to determine the stereochemistry of the substituents on the ring, the alcohol was converted to its 3,5-dinitrobenzoate derivative and submitted for X-ray analysis (Figure 1).# It was found that the hydroxyl group and the cyclopropane are syn to each other and that the ester group, not unexpectedly, is in the exo configuration

The presence of the ester on the cyclopropane was dictated by our wish to have a carboxyl group in the final product, and had the added advantage of controlling the regiochemistry of cyclopropane opening.[62]

Only low angle diffraction data were collected.

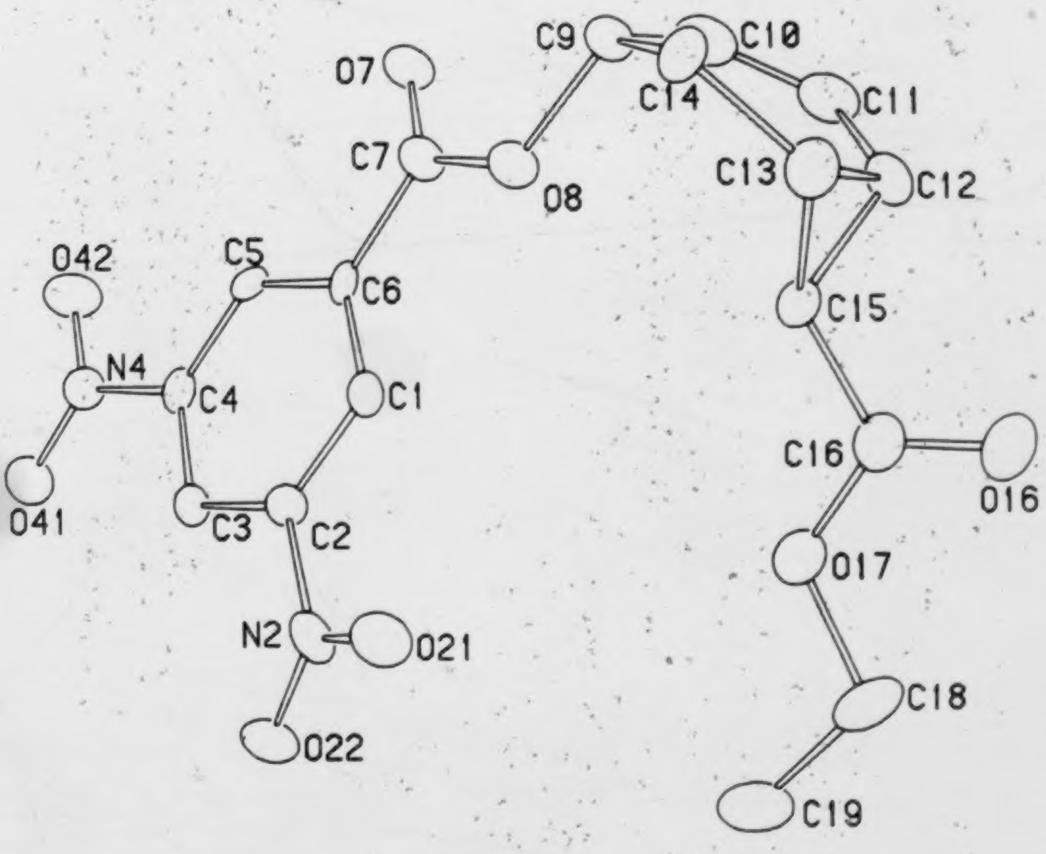
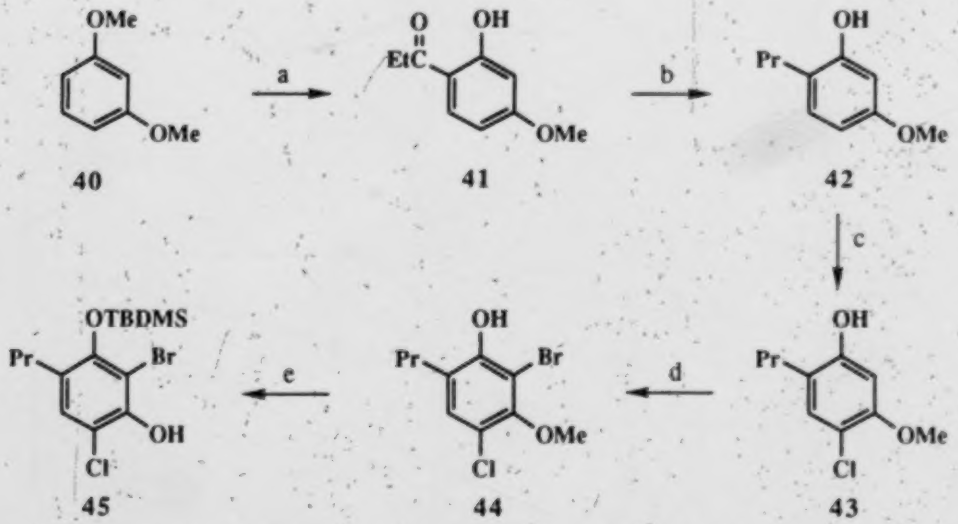

C9
C10
O7
C14
C11
C7
C13
C12
O8
O42
C5
C6
C15
N4
C4
C1
C16
O41
C3
C2
O16
O17
N2
O21
C18
O22
C19

Figure 1. X-ray crystal structure of the 3,5-dinitrobenzoate derivative of 34

With the alcohol **34** in hand, its coupling with phenol **33** was conducted and led to the desired product **35** in 33% yield (Scheme 4). Although, the yield was poor, no optimization was attempted as the coupled product **35** served only to test the free radical conversion to **36**. Treatment of **35** with stannane and triethylborane in the presence of air[50] gave the desired tricyclic compound **36** in 67% yield. Since the reaction proceeded satisfactorily, the sequence was repeated using the more substituted phenol **45** (Scheme 6).

SCHEME 6


OMe
OMe
40
a
O
EtC
OH
OMe
41
b
Pr
OH
OMe
42
c
OH
Pr
OMe
Cl
43
d
OH
Pr
Br
OMe
Cl
44
e
OTBDMS
Pr
Br
OH
Cl
45

Scheme 6. Reagents and conditions: (a) EtCOCl, $AlCl_3$, 2 h; then dilute HCl, 47%; (b) Zn(Hg), conc HCl, reflux, 1.5 h, 88%; (c) SO_2Cl_2, ether, 1.5 h, 70%; (d) Br_2, AcOH, 45 min, *ca* 92%; (e) TBDMSCl, imidazole, DMF; (f) BBr_3, CH_2Cl_2, -78 °C, 82% overall.

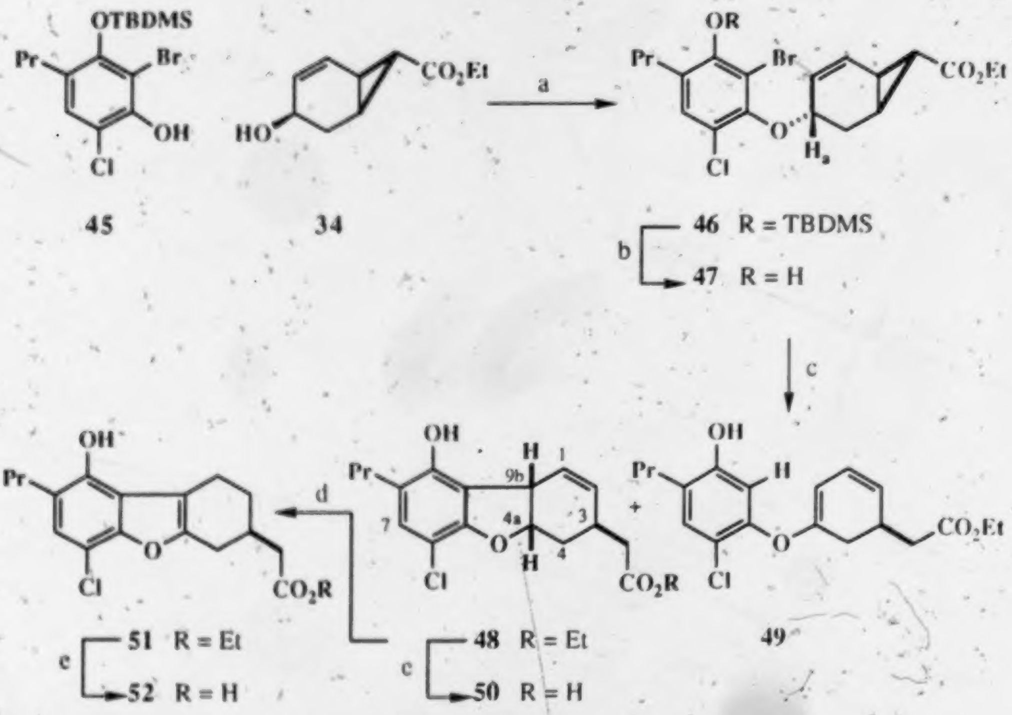
The choice of the substituents on the latter was made in such a way that the benzofuran derivative eventually produced, would ressemble other previously studied benzofurans,[58] which had been found to inhibit leukotriene biosynthesis.

Compound **45** was synthesized as follows: (Scheme 6). Friedel-Crafts acylation of dimethoxybenzene[63] with propionyl chloride gave propiophenone **41**, which was reduced with amalgamated zinc in concentrated hydrochloric acid[64] to afford the corresponding propylphenol **42**. Chlorination (sulfuryl chloride) and then, bromination (bromine/acetic acid) led to **44**[65] in good overall yield (63%). Silylation followed by deprotection of the phenol (boron tribromide) gave **45** (82%), which is suitably set up for the coupling step.

Mitsunobu coupling of **45** with alcohol **34** gave the desired product **46** in very good yield (80%) providing that activation of the alcohol was done at -30 to -20 °C, and not at a higher temperature, in which case elimination of the hydroxyl group is a competing process (Scheme 7).

The stereochemistry of **46** (and also of **35**) is a tentative assignment based on the assumption that inversion occurs. Desilylation (TBAF) of **46**, and treatment of **47** with stannane, under the conditions used for **36**, led to the desired product **48** (43%), together with a minor byproduct **49** (18%). Evidence in favor of such an assignment for **48** was obtained on the basis of the following considerations:

SCHEME 7


OTBDMS
Pr
Br
OH
Cl
45
HO
CO₂Et
34
a
OR
Pr
Br
O
Cl
Hₐ
CO₂Et
46 R = TBDMS
b
47 R = H
c
OH
Pr
O
Cl
CO₂R
51 R = Et
e
52 R = H
d
OH
Pr
H
9b
1
4a
3
7
O
H
4
Cl
CO₂R
48 R = Et
e
50 R = H
+
OH
Pr
H
O
Cl
CO₂Et
49

Scheme 7. Reagents and conditions: (a) DEAD, Ph_3P, THF, -30 to -20 °C, 2 h; (b) TBAF, THF, 1.5 h, 64% overall; (c) Bu_3SnH, Et_3B, benzene, 24 h, 43% of 48 and 18% of 49; (d) $RhCl_3.3H_2O$, EtOH-benzene, 65 °C, 18 h, 84%; (e) LiOH, THF-water, 8 h, *ca* 100%.

The ^1H NMR spectrum, which was complemented by decoupling experiments, showed two sets of olefinic signals at δ 5.76 and δ 5.88, and these signals were coupled (J = 10.2 Hz) to each other with a coupling constant in the expected range for cis geometry at C-4a and C-9b. The aromatic proton at C-7 was still present [at δ 6.86 (s)]. The hydrogen at C-4a (adjacent to the oxygen of the furan ring) resonated at δ 5.08--5.18 (m) and was coupled (J = 8.0 Hz) with the adjacent C-9b bis-allylic methine proton (δ 3.98), as shown by irradiation of either signal.

Finally, the signal characteristic of the methine hydrogen at C-3 resonated at δ 2.89 (m) and, as expected, irradiation of the latter caused the signal (δ 5.88) corresponding to the C-2 olefinic hydrogen to collapse to a dd (J = 10.0, 3.2 Hz). It will be noted that, although the junction of the dihydrofuran ring (C-4a and C-9b) can be assigned with confidence as being *cis*, the stereochemistry of the CH_2CO_2Et substituent is tentatively assigned on the assumption that the stereochemistry for the precursor **46** results from the expected inversion in the Mitsunobu coupling.

The formation of **49** presumably arises by intramolecular abstraction of H_a in **47**, by the benzene radical resulting from homolytic cleavage of the carbon-bromine bond (Scheme 7), to form an intermediate radical which then collapses to give the observed product.

It will be noted that the radical closure-ring opening reaction was conducted under high dilution (0.01 M in substrate; 0.02 M in stannane) to compensate for the fact that the stannane is added in one portion. Under these conditions, no product coming from simple reduction of the bromide was observed and the chlorine atom present on the benzene ring survived.

Isomerization of **48** with rhodium chloride monohydrate under carefully defined conditions[66] gave **51** in excellent yield (84%). Both **48** and **51** were hydrolysed to the corresponding carboxylic acids **50** and **52**, respectively, and these were then evaluated for inhibition of leukotriene biosynthesis. Unfortunately, only marginal activity was found.[#]

[#] We thank Merck Frosst Canada for the bioassay, which was done by the method of reference 58. Compound **52**: 13% inhibition of leukotriene biosynthesis at 1 μg/mL; compound **50**: 17% inhibition at 1 μg/mL.

2) Conclusion

We have demonstrated that radical ring opening of cyclopropanes can be used by itself and that the method can be combined with the well documented radical cyclization to provide a radical closure-ring opening sequence.

An extension of this work could be a process whereby a series of radical closure and ring openings, which do not necessarily involve the formation of benzofurans, would be combined together to afford a reaction commonly called a 'zip' reaction. This would lead to interesting polycyclic compounds. We have not yet had the opportunity to investigate such processes.

III. EXPERIMENTAL

Unless otherwise stated the following particulars apply. Reactions involving water-sensitive reagents were carried out under argon, purified by passage through a column (3.5 x 42 cm) of R-311 catalyst# and then through a similar column of Drierite.

Glassware was dried in a oven for at least 3 h (140 °C), cooled in a desiccator, quickly assembled, and sealed with rubber septa (when applicable). Inlet and exit needles for argon were passed through a septum on the apparatus, and argon was purged through the system. The exit needle was then removed, and the apparatus was kept under a static pressure of argon. Stirring was effected by using a dry Teflon-coated magnetic stirring bar. Isolated compounds were homogeneous as judged by ^{1}H NMR measurements. When a solution was injected over a specified time, the time refers to the main volume of the solution and not to the solvent used as a rinse; the latter was usually injected at a fast dropwise rate.

Solvents were distilled before use for chromatography or extractions. Where required, solvents and reagents were dried with suitable drying agents and distilled under argon, except for hexane and methanol, which were protected from moisture using a calcium sulfate drying tube.

Products were isolated from solution by concentration under water pump vacuum at 30 °C using a rotary evaporator. Where compounds were

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#Supplied by chemicals Dynamics Corp., South Plainfield, N. J.

isolated by simple evaporation of their solutions, the residues were kept under vacuum (<0.1mm) until of constant weight. Melting points were measured with a Kofler block melting point apparatus. Boiling points reported for products distilled in a Kugelrohr apparatus refer to the oven temperature. Commercial silica (Merck 60F-254) thin layer chromatography (TLC) plates were used. Silica gel for flash column chromatography was Merck type 60 (230-400 mesh). Products isolated after flash chromatography were homogeneous (TLC, and/or ^{1}H NMR). Alumina for column chromatography was neutral and of grade III. TLC plates were examined under UV radiation (254 nm), treated with iodine vapor, and/or charred on a hot plate after being sprayed with a solution of phosphomolybdic acid.[#] or anisaldehyde.[##]

All vapor phase chromatographic (VPC) analyses were performed on a Hewlett-Packard 5830A gas chromatograph equipped with an FID detector using prepacked Hewlett-Packard 6ft x 1/8 in o.d. stainless steel analytical columns with nitrogen as the carrier gas: The specification of the column used for vapor phase chromatographic analysis was 10% OV-1, 80/100 Chromosorb W-HP. A Branson ultrasonic bath (Model B-12) was used as a source of ultrasound.

[#] Anisaldehyde (15 drops) in a mixture of 95% ethanol (94 mL) and concentrated sulfuric acid (6 mL).

[##] Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (485 mL) and concentrated sulfuric acid.

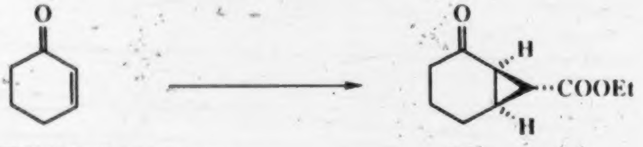
Elemental combustion analyses were performed in the microanalytical laboratories of the University of Alberta. An X-ray crystal structure was determined by Dr. B. Santarciero at the University of Alberta. Infrared spectra were recorded with a Perkin-Elmer 297 spectrophotometer or a Nicolet 7000 FT-IR model. Liquids and solids were run as solutions in the specified solvent in 0.5-mm potassium bromide cells. Proton NMR spectra were recorded with a Bruker WP-80 (at 80 MHz), WP-200 (at 200 MHz), Bruker AM-300 (at 300 MHz), or Bruker AM-400 (at 400 MHz) spectrometer in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded with a Bruker AM-300 (at 75.5 MHz) or Bruker AM-400 (at 100.6 MHz) spectrometer in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. Where indicated, the assignment of resonances to carbon type was determined using the APT[69,70] sequence. The following abbreviations are used in the text: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; J, coupling constant; δ, chemical shift. Mass spectra were recorded on an AEI MS-12 or MS-50 mass spectrometer at an ionizing voltage of 70 eV.

Materials. Dry 1,2-dimethoxyethane (DME), dioxane, tetrahydrofuran, ether, and benzene were distilled from sodium-benzophenone ketyl; dry carbon tetrachloride, chloroform, dichloromethane, hexane, pyridine, toluene, and triethylamine were distilled from calcium hydride. Dry DMSO and dimethylaniline were distilled from calcium hydride under reduced pressure (15 mm). Dry diglyme was distilled from calcium hydride and then from lithium aluminum hydride under reduced pressure (40 mm). Dry dimethylformamide (DMF) was distilled from molecular sieves 4Å under reduced pressure (40 mm). Dry methanol was distilled shortly before use from magnesium. Anhydrous ethanol was commercial dehydrated ethanol from U.S. Industrial Chemicals Co. Azobis(iso-butyronitriie) (AIBN) from Eastman was used without further purification and stored at 5°C.

General procedure for photochemical radical ring-opening. The substrate was placed in a 10- or 25-mL oven-dried Pyrex flask with an optically flat panel in its upper side and containing a Teflon-coated stirring bar. The system was flushed with argon, and dry solvent was injected. The flask was lowered into a cold-bath (-70 °C to 0 °C, depending on the experiment) and irradiated from above with a 275 W General Electric Sunlamp. Triphenyltin hydride (or tributyltin hydride) (1.5 equiv) was injected over a period of 1 min and stirring was continued for 0.5 to 4 h at the specified temperature. The mixture was transferred to a round-bottomed flask and evaporated, and the residue was then processed as described for the individual examples.

General procedure for thermal radical ring-opening. The substrate was placed in a 10- or 25-mL oven-dried round-bottomed flask containing a Teflon-coated stirring bar and equipped with a reflux condenser sealed by a rubber septum. The system was flushed with argon for 5-10 min, and dry benzene was injected. Triphenyltin hydride (or tributyltin hydride) (1.5 equiv) was injected over 1 min and AIBN (0.1 equiv) was added in one portion. The flask was lowered into an oil bath preheated to 100 °C, and the mixture was refluxed for 0.25 to 3 h, after which it was cooled and evaporated. The residue was then processed as described for the individual examples.

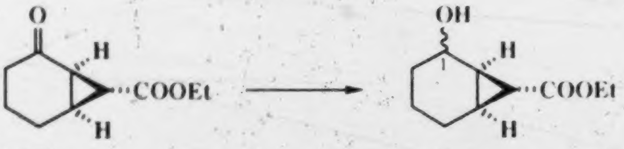
Ethyl (1α,6α,7α)-2-Oxobicyclo[4.1.0]heptane-7-carboxylate (11b).



11a **11b**

Ethyl (dimethylsulfuranylidene)acetate[41] (2.94 g, 19.9 mmol) was injected over 4 h into a refluxing solution of 2-cyclohexen-1-one (957 mg, 9.95 mmol) in dry benzene (9 mL). Refluxing was continued for an additional 14 h, and the solvent was then evaporated. Flash chromatography of the residue over silica gel (6.5 cm x 20 cm) using first 10% ethyl acetate--hexane and then gradually increasing proportions of ethyl acetate (up to 40%) afforded slightly impure (TLC, silica, 25% ethyl acetate--hexane) **11b** (1.44 g). Distillation (Kugelrohr; 100 °C, 0.08 mm) gave pure (TLC, 25% ethyl acetate--hexane) **11b** (1.32 g, 73%) as a white solid: FT-IR ($CHCl_3$ cast) 2940, 1725, 1700, 1295, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, J = 7.0 Hz, 3 H), 1.65 (m, 1 H), 1.81 (m, 1 H), 1.92--2.26 (m, 4 H), 2.24--2.38 (m, 3 H), 4.17 (q, J = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.07, 18.06, 20.34, 23.55, 24.66, 33.49, 36.91, 61.07, 171.09, 205.07; exact mass, *m/z* calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0942. Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.49; H, 7.59.

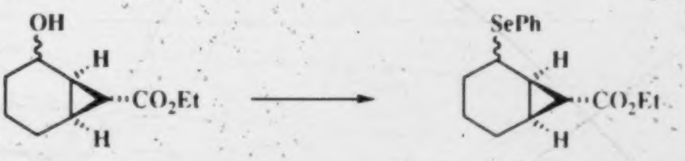
Ethyl (1α,2β,6α,7α)- and (1α,2α,6α,7α)-2-Hydroxybicyclo[4.1.0]heptane-7-carboxylate (11c).



11b **11c**

Sodium borohydride (109 mg, 2.87 mmol) was added over 3 min to a cold (0 °C) and stirred suspension of **11b** (476 mg, 2.61 mmol) and cerium trichloride heptahydrate (1.09 g, 2.92 mmol) in methanol (7 mL). Stirring was continued for 30 min. The mixture was quenched by addition of water (10 mL), and extracted with ether (2 x 25 mL). The combined organic extracts were washed with brine (1 x 15 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm) using 40% ethyl acetate--hexane gave alcohols **11c** (410 mg, 85%) as a colorless oil: FT-IR ($CHCl_3$ cast) 3430, 2940, 1720, 1700, 1300, 1175, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (m, 1 H), 1.10--1.20 [m, including a triplet at 1.27 (J = 7.3 Hz), 11 H], 2.23 (broad m, 0.41 H), 2.60 (broad s, 0.61 H), 4.04 (broad s, 0.8 H), 4.12 (two superimposed quartets, J = 7.3 Hz, 2 H), 4.21 (m, 0.2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major isomer) δ 14.22, 15.84, 21.97, 22.01, 24.21, 29.01, 30.21, 60.47, 65.80, 174.00; (minor isomer) δ 20.09, 21.89, 22.70, 23.99, 28.92, 29.75, 65.63, 174.11; exact mass, *m/z* calcd for $C_{10}H_{15}O_2$ 167.1052, found 167.1072. Anal. Calcd for $C_{10}H_{15}O_2$: C, 65.19; H, 8.76. Found: C, 65.38; H, 8.67.

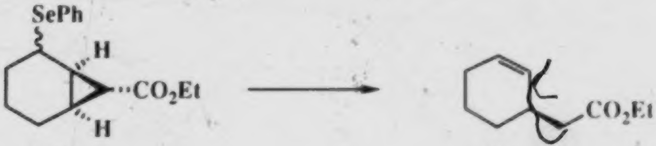
Ethyl (1α,2α,6α,7α)- and (1α,2β,6α,7α)-2-(Phenylseleno)bicyclo-[4.1.0]heptane-7-carboxylate (11d).



11c **11d**

Phenylselenocyanate (982 mg, 5.4 mmol) and then tributylphosphine (1.34 mL, 5.4 mmol) were added, each in one portion, to a cold (0 °C) and stirred solution of **11c** (332 mg, 1.8 mmol) in dry THF (7 mL). Stirring was continued for 4 h at 0 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm) using successively hexane, 50% dichloromethane--hexane, and 5% ethyl acetate--hexane gave **11d** (468 mg, 80%) as a slightly yellow oil: FT-IR ($CHCl_3$ cast) 2935, 1720, 1575, 1300, 1182, 740, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15 [m, including two superimposed triplets at 1.25 (J = 7.2 Hz), 5 H], 3.62 (m, 0.2 H), 3.79 (m, 0.8 H), 4.10 (two superimposed quartets, J = 7.2 Hz, 2 H), 7.25 (m, 3 H), 7.58 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major isomer only) δ 14.20, 21.88, 22.17, 24.89, 25.56, 27.60, 28.39, 39.22, 60.28, 127.50, 128.78, 135.15, 173.65; exact mass, *m/z* calcd for $C_{16}H_{20}O_2Se$ 324.0629, found 324.0629. Anal. Calcd for $C_{16}H_{20}O_2Se$: C, 59.44; H, 6.24; O, 9.90. Found: C, 59.74; H, 6.28.

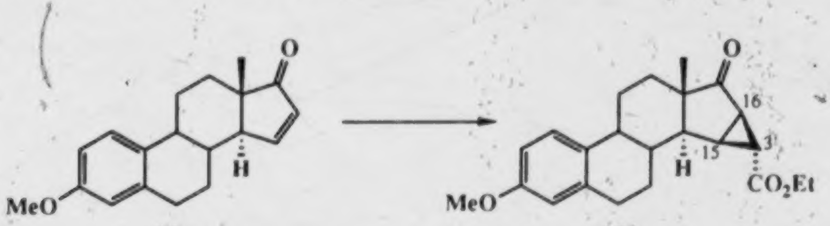
Ethyl (2-Cyclohexen-1-yl)acetate (11e).



11d **11e**

The general procedure for thermal radical ring opening was followed using **11d** (179 mg, 0.55 mmol) in dry benzene (5.5 mL), triphenyltin hydride (183 µL, 0.72 mmol), and AIBN (4 mg, 0.03 mmol). Refluxing was continued for 1 h and the mixture was then evaporated. Kugelrohr distillation (90 °C, 1.5 mm) of the residue afforded **11e** (85.4 mg, 92%) as a colorless oil: FT-IR ($CHCl_3$ cast) 2920, 1740, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19--1.38 [m, including a triplet at 1.27 (J = 7.2 Hz), 4 H], 1.45--1.92 (m, 4 H), 2.0 (m, 2 H), 2.28 (m, 2 H), 2.60 (m, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.55 (ddd, J = 10.1 Hz, 4.1, 2.5 Hz, 1 H), 5.72 (ddd, J = 10.1, 5.6, 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.30, 21.01, 25.05, 28.83, 32.31, 40.90, 60.23, 128.11, 130.19, 172.84; exact mass, *m/z* calcd for $C_{10}H_{16}O_2$ 168.1151, found 168.1151. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.08; H, 9.27.

Ethyl (15α,16α)-Dihydro-3-methoxy-17-oxo-3'*H*-cycloprop[15,16]estra-1,3,5,(10),15-tetraenyl-3'-carboxylate (12b).[#]

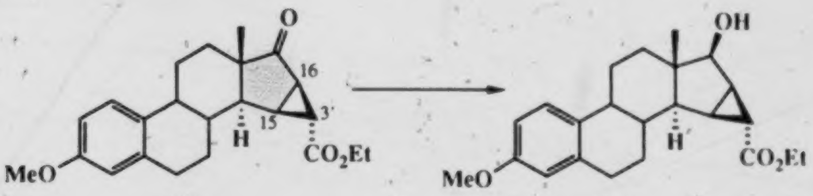


12a **12b**

Ethyl (dimethylsulphuranylidene)acetate[41] (663 mg, 4.48 mmol) was added with stirring over 3 h (syringe pump) to a warm (55 °C) solution of **12a** (633 mg, 2.24 mmol) in dry DMSO (7.4 mL). Stirring at 55 °C was continued for 18 h, and water (20 mL) was added. The mixture was extracted with dichloromethane (50 mL) and the organic extract was washed with 1:1 brine-water (1 x 50 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.0 x 20 cm) using 20% ethyl acetate--hexane afforded impure **12b** (546 mg). The material, which was used directly in the next step, had: ^1H NMR ($CDCl_3$, 200 MHz) (major and most characteristic signals only) δ 0.98 (s, about 2.1 H), 1.04 (s, 0.65 H), 1.28 (t, J = 7.6 Hz), 3.76 (s, 3 H), 4.15 (dq, J = 7.6, 2.4 Hz, 2 H), 6.65 (d, J = 2.8 Hz, 1 H), 6.71 (d, J = 8.0, 2.8 Hz, 1 H). 7.16 (d, J = 8.0 Hz, 1 H).

[#] Stereochemistry shown at C(3') is an arbitrary assignment; that at C(15) and C(16) is made by analogy to the transformation **18a→18b**

Ethyl (15α,16α)-Dihydro-17-hydroxy-3-methoxy-3'*H*-cycloprop[15,16]-estra-1,3,5,(10),15-tetraenyl-3'-carboxylate (12c).#

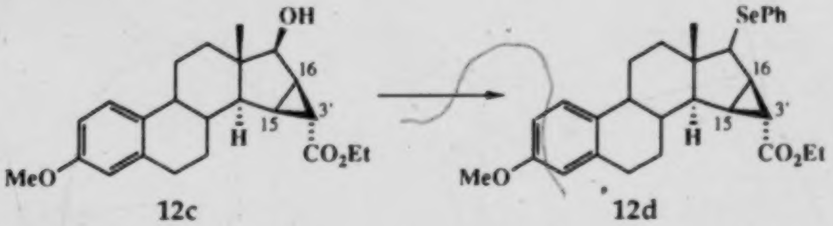


12b **12c**

Sodium borohydride (66 mg, 1.75 mmol) was added over 3 min to a stirred suspension of crude **12b** (536 mg, 1.45 mmol) and cerium trichloride heptahydrate (652 mg, 1.75 mmol) in methanol (7 mL). Stirring was continued at room temperature for 2 h. Further portions of cerium trichloride heptahydrate (325 mg, 0.88 mmol) and of sodium borohydride (33 mg, 0.88 mmol) were then added and stirring was continued for 1 h. The mixture was quenched by addition of water (1 x 10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined extracts were washed with water (1 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm) using first 20% ethyl acetate--hexane and then 25% ethyl acetate--hexane gave crude **12c** (471 mg), which was used directly in the next step. The material had: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 0.37 H), 0.86 (s, 1.56 H), 0.88 (s, 0.55 H), 1.04 (s, 0.25 H), 1.27 (t, J = 7.3 Hz, 3.7 H), 1.32--1.70 (m, 4.5), 1.71--2.04 (m, 4.1), 2.05--2.40 (m, 4 H), 2.73--3.0 (m, 2.2 H), 3.78 (s, 3.06 H), 4.12 (m, 2.5 H), 6.65 (d, J = 2.9) and 6.71 (dd, J = 8.4, 2.9 Hz) [both signals together correspond to 2.0 H], 7.12--7.25 [m, including doublet at 7.17 (J = 8.4 Hz), 1.06 H].

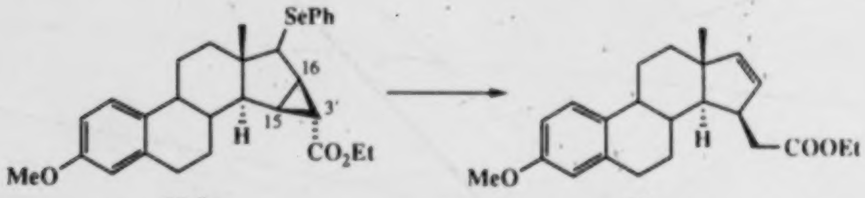
#Stereochemistry shown at C(3') is an arbitrary assignment; that at C(15), C(16) and C(17) is made by analogy to the transformation **18a→18b→18c**.

Ethyl (15α,16α)-Dihydro-3-methoxy-17-(phenylseleno)-3'*H*-cycloprop-[15,16]estra-1,3,5,(10),15-tetraenyl-3'-carboxylate (12d).



Phenylselenocyanate (263 mg, 1.45 mmol) in dry THF (1 mL) was added with stirring over 2 h (syringe pump) to a warm (45 °C) solution of crude **12c** (268 mg, 0.723 mmol) and tributylphosphine (361 μL, 1.45 mmol) in dry THF (4 mL). Stirring was continued at 45 °C for 16 h and the solvent was evaporated. Flash chromatography of the residue over silica gel (2.0 x 20.0 cm) using first 30% dichloromethane--hexane (to remove diphenyl diselenide) followed by 15% ethyl acetate--hexane afforded a mixture of selenides **12d** in a ratio of 95:5 [^{1}H NMR (300 MHz)] (218 mg, 59% based on unsaturated estrone **12a**) as a gummy white solid: FT-IR ($CHCl_3$ cast) 2932, 1722, 1500, 1282, 1172, 1037, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 0.3 H), 1.0 (s, 2.7 H), 1.21 (t, J = 7.3 Hz, 3 H), 1.36--1.68 (m, 4 H), 1.74--2.46 (m, 8 H), 2.82--3.0 (m, 2 H), 3.74 (s, 3 H), 3.80 (s, 1 H), 4.06 (q, J = 7.3 Hz, 2 H), 6.63 (d, 2.9 Hz, 1 H), 6.70 (dd, J = 8.5, 2.9 Hz, 1 H), 7.14 (d, J = 8.5 Hz, 1 H),7.20--7.32 (m, 3 H), 7.50--7.69 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major peaks only) δ 14.22, 24.36, 26.46, 26.75, 28.09, 28.40, 29.57, 31.34, 37.06, 41.07, 42.04, 44.08, 52.83, 55.19, 56.78, 60.51, 111.45, 113.87, 125.90, 127.20, 129.13, 130.23, 132.30, 133.83, 137.72, 157.60, 172.72; exact mass, *m*/*z* calcd for $C_{29}H_{34}O_3Se$ 510.1674, found 510.1672. Anal. Calcd for $C_{29}H_{34}O_3Se$: C, 68.36; H, 6.73; O, 9.43. Found: C, 68.17; H, 6.82; O, 9.37.

Ethyl (3-Methoxyestra-1,3,5(10),16-tetraen-15β-yl)acetate (12e).#

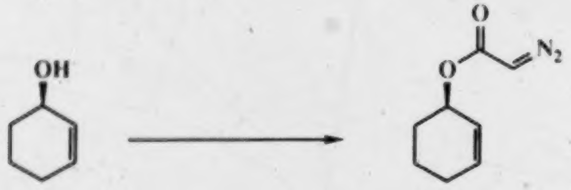


12d **12e**

With one modification, the general procedure for thermal radical ring opening was followed using selenides **12d** (129 mg, 0.252 mmol) in benzene (2.5 mL), tributyltin hydride (88 μL, 0.33 mmol), and AIBN (3 mg, 0.02 mmol). In this particular experiment, further portions of tributyltin hydride (88 μL, 0.33 mmol) and AIBN (3 mg, 0.02 mmol) were added after 4 h, since the reaction had stopped (TLC control, silica, 10% ethyl acetate--hexane). Stirring under reflux was continued for 12 h more. The mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (1.5 x 20.0 cm) using 10% ethyl acetate--hexane afforded pure **12e** (80 mg, 90%) as a white solid: FT-IR ($CHCl_3$ cast) 3248, 1733, 1500, 1255; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.97 (s, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.43--1.70 (m, 4 H), 1.71--1.88 (m, 2 H), 1.95 - 2.09 (m, 1 H), 2.20--2.41 (m, 3 H), 2.56 (dd, J = 15.6, 3.6 Hz, 1 H), 2.80--2.98 (m, 2 H), 2.98--3.08 (m, 1 H), 3.78 (s, 3 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.89 (dd, J = 6.0, 3.0 Hz, 1 H), 5.97 (d, J = 6.0 Hz, 1 H), 6.66 (d, J = 2.9 Hz, 1 H), 6.72 (dd, J = 8.8, 2.9 Hz, 1 H), 7.18 (J = 8.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.30, 22.26, 26.02, 27.61, 29.58, 35.20, 35.42, 37.58, 40.83, 45.12, 46.39, 55.21, 55.79, 60.35, 111.34, 113.84, 125.70, 132,95, 133.12, 137.62, 143.67, 157.58, 173.32; exact mass, *m/z* calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2193. Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.96; H, 8.25.

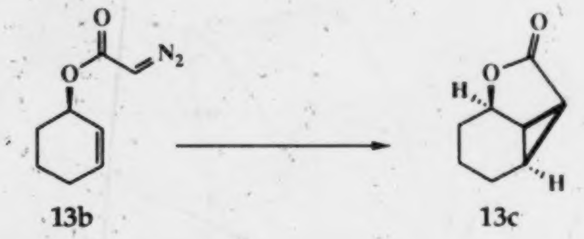
#Stereochemistry at C(15) follows from the sense of cyclopropanation

2-(Cyclohexen-1-yl)diazoacetate (13b).


13a 13b

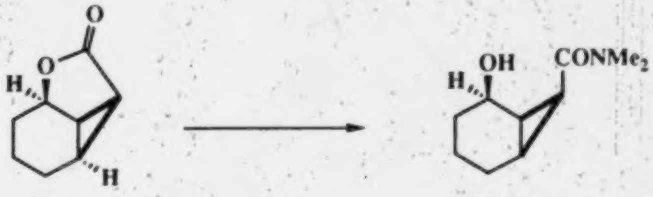
The procedure is based on a general literature method.[35] Dry *N,N*-dimethylaniline (1.55 mL, 12.24 mmol) was added to a cold (0 °C) and stirred solution of 2-cyclohexen-1-ol (1.0 g, 10.2 mmol) and [(*p*-toluenesulfonyl)hydrazono]acetyl chloride[69] (3.31 g, 12.75 mmol) in dry dichloromethane (68 mL). After 20 min at 0 °C, dry triethylamine (7.1 mL, 51 mmol) was injected over about 1 min and stirring was continued for 15 min. The cold-bath was removed, and after a further 30 min, the mixture was quenched with water (30 mL), and concentrated. The residue was extracted with 10% ethyl acetate--hexane (2 x 65 mL) and the combined extracts were washed with saturated aqueous citric acid (2 x 30 mL). The combined aqueous layers were extracted with 10% ethyl acetate--hexane (1 x 30 mL), and the organic extract was washed with saturated aqueous citric acid (1 x 5 mL). All the organic extracts were combined, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm) using 8% ethyl acetate--hexane afforded **13b** (1.19 g, 70%) as a bright yellow oil, containing trace impurities. The material was distilled (Kugelrohr, 45 °C, 0.05 mm) for characterization: FT-IR ($CHCl_3$ cast) 3120, 2950, 2055, 1690, 1380, 1180; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55--1.81 (m, 3 H), 1.81--2.18 (m, 3 H), 4.74 (broad s, 1 H), 5.35 (m, 1 H), 5.72 (ddt, J = 10.0, 3.8, 2.1 Hz, 1 H), 5.96 (ddt, J = 10.0, 3.8, 1.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.60, 24.86, 28.49, 68.61, 125.68, 132.67; exact mass, *m/z* calcd for $C_8H_{10}N_2O_2$ 166.0742, found 166.0725. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.06; N, 16.86. Found: C, 57.81; H, 5.98; N, 16.81.

(2aα,2bα,5aα,5bα)-Hexahydrocyclopropa[cd]benzofuran-2(2a*H*)-one (13c).



A solution of **13b** (1.09 g, 6.56 mmol) in dry toluene (40 mL) was injected over 12 h into a refluxing solution of bis-(*N*-*tert*-butyl salicylaldiminato)copper(II)[70] (136 mg, 0.328 mmol) in dry toluene (210 mL) contained in a 500-mL round bottomed flask equipped with a condenser and heated by an oil bath set at 135 °C. After the addition was complete the mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm) using 40% ethyl acetate--hexane afforded **13c** (798 mg, 88%) as a slightly yellow oil: FT-IR ($CHCl_3$ cast) 2950, 1760, 1340, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40--1.78 (m, 5 H), 1.85 (m, 1 H), 2.08 (m, 2 H), 2.36 (dt, J = 8.0, 6.2 Hz, 1 H), 4.92 (dt, J = 6.0, 2.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.61, 18.07, 18.52, 22.60, 24.07, 24.70, 74.03, 175.69; exact mass, *m/z* calcd for $C_8H_{10}O_2$ 130.0681, found 130.0682. Anal. Calcd for $C_8H_{10}O_2$: 69.54; H, 7.29. Found: C, 69.18; H, 7.31.

(1α,2β,6α,7β)-2-Hydroxy-*N*,*N*-dimethylbicyclo[4.1.0]heptane-7-carboxamide (13d).

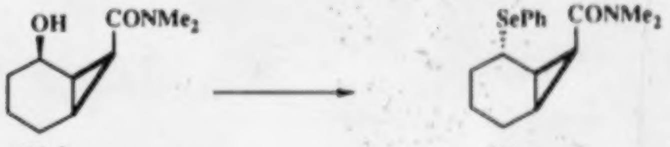


13c **13d**

The procedure is based on a general literature method.[36] Cold (-70 °C) dimethylamine (30 μL, 0.456 mmol) and then trimethylaluminum (2 M in toluene, 0.217 mL, 0.434 mmol) were added to dry dichloromethane (1 mL) contained in a 10-mL round-bottomed flask equipped with a condenser. The mixture was stirred for 30 min at room temperature and lactone **13c** in dry dichloromethane (0.2 mL, plus 0.2 mL as a rinse) was injected over about 5 min. Stirring was continued for 3 h at room temperature and then at reflux for 5 h. The mixture was cooled in ice and quenched by careful addition of aqueous hydrochloric acid (1 M, 0.5 mL). The aqueous layer was extracted with dichloromethane (2 x 7 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Kugelrohr distillation (90 °C, 0.05 mm) afforded **13d** (37 mg, 93%) as a white solid: FT-IR ($CHCl_3$ cast) 3287, 2943, 2870, 1615, 1451, 1048, 711 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (m, 1 H), 0.97 (m, 1 H), 1.13 (ddq, J = 13.0, 4.5, 2.2 Hz, 1 H), 1.43 (dm, J = 13.0 Hz, 1 H), 1.77 (m, 2 H), 1.94 (m, 2 H), 3.03 (s, 3 H), 3.17 (s, 3 H), 4.12 (tt, J = 11.0, 7.0 Hz, 1 H), 5.30 (d, J = 11.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.79, 20.00, 20.21, 22.53, 25.84, 31.71, 35.41, 37.57, 66.65, 171.16; exact mass, *m/z* calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1256. Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.41; H, 9.20; N, 7.84.

In a similar experiment done on a bigger scale [**13c** (150 mg)], **13d** (180 mg, 90%) was obtained.

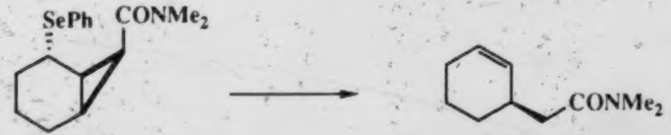
(1α,2α,6α,7β)-*N*,*N*-Dimethyl-2-(phenylseleno)bicyclo[4.1.0]heptane-7-carboxamide (13e).



13d **13e**

Phenylselenocyanate (236 μL, 1.75 mmol) in dry THF (0.5 mL) was added over 15 min (syringe pump) to a refluxing solution of **13d** (168 mg, 0.874 mmol) and tributylphosphine (436 μL, 1.75 mmol) in dry THF (3.9 mL) contained in a 10-mL round-bottomed flask equipped with a condenser. Stirring was continued for 14 h and the mixture was cooled and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) using 40% ethyl acetate--hexane gave **13e** (232 mg, 78%) as an orange oil. The material contained slight impurities [^{1}H NMR (200 MHz)] but was suitable for the next stage: FT-IR ($CHCl_3$ cast) 2930, 2855, 1841, 1580, 1140, 740, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.2 (m, 1 H), 1.34--1.63 (m, 5 H), 1.75 (m, 2 H), 1.88 (m, 1 H), 2.93 (s, 3 H), 3.04 (s, 3 H), 4.0 (ddd, J = 8.1, 5.1, 2.3 Hz, 1 H), 7.25 (m, 3 H), 7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 15.18, 19.57, 20.34, 21.50, 22.85, 28.97, 34.89, 36.17, 37.02, 127.08, 128.98, 130.37, 133.97, 170.24; exact mass, *m*/*z* calcd for $C_{16}H_{21}NOSe$ 323.0789, found 323.0791. Anal. Calcd for $C_{16}H_{21}NOSe$: C, 59.62; H, 6.57; N, 4.34. Found: C, 59.45; H, 6.51; N, 4.45.

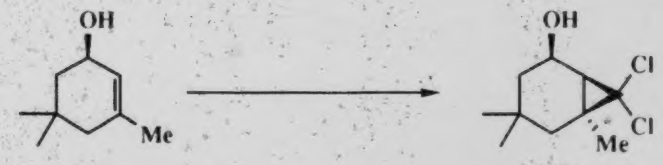
N,N-Dimethyl-2-cyclohexene-1-acetamide (13f).



13e **13f**

With one exception, the general procedure for thermal radical ring opening was followed using selenide **13e** (221 mg, 0.685 mmol) in benzene (6.8 mL), triphenyltin hydride (262 μL, 1.02 mmol), and AIBN (11 mg, 0.07 mmol). In this particular experiment a second portion of AIBN (11 mg, 0.07 mmol) was added after 30 min at reflux temperature. Refluxing was continued for 2 h after the second addition of initiator, and the mixture was then cooled and evaporated. Kügelrohr distillation of the residue (90 °C, 0.4 mm) afforded **13f** (109 mg, 96%) as a colorless oil: FT-IR ($CHCl_3$ cast) 3020, 2924, 1647, 1395, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (m, 1 H), 1.51--1.78 (m, 2 H), 1.85 (m, 1 H), 1.97 (m, 2 H), 2.3 (m, 2 H), 2.69 (m, 1 H), 2.96 (s, 3 H), 3.03 (s, 3 H), 5.59 (dm, J = 10.0 Hz, 1 H), 5.72 (ddd, J = 10.0, 5.9, 3.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 21.12, 25.18, 29.14, 32.25, 35.42, 37.46, 39.41, 127.70, 131.07, 172.10; exact mass, *m/z* calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1308.

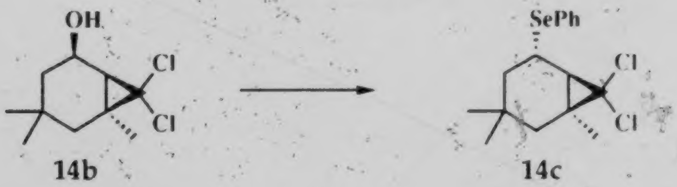
(1α,2β,6α)-7,7-Dichloro-4,4,6-trimethylbicyclo[4.1.0]heptan-2-ol (14b).



14a **14b**

Benzyltriethyl-ammonium chloride (35 mg) was added to a cold (0 °C) and stirred solution of 3,5,5-trimethyl-2-cyclohexen-1-ol (1.0 g, 7.13 mmol) in chloroform (15 mL). Aqueous sodium hydroxide 50% w/w (7.1 mL) was then added over a period of 5 min.[34] The course of the reaction was closely monitored by TLC (silica, 20% ethyl acetate hexane),[#] and, after 40 min at 0 °C, the reaction was stopped by addition of water (15 mL), and ether (25 mL) was added. The aqueous layer was extracted with ether (2 X 25 mL) and the combined organic layers were dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.0 cm X 20.0 cm) using 15% ethyl acetate--hexane gave **14b** (1.14 g, 71%) as a white solid: FT-IR ($CHCl_3$ cast) 3220, 2956, 1050, 843 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3 H), 0.95 (s, 3 H), 1.24 (dd, J = 12.3, 11.8 Hz, 1 H), 1.41 (s) and 1.44 (dd, J = 14.5, 2.1 Hz) [both signals together correspond to 4 H], 1.61 (ddd, J = 13.1, 7.5, 2.1 Hz, 1 H), 1.69 (d, J = 7.5 Hz) and 1.75 (dd, J = 14.5, 0.7 Hz) [both signals together correspond to 2 H], 1.97 (broad s, 1 H), 4.32 (dt, J = 11.2, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 25.21, 25.99, 30.95, 32.04, 32.56, 36.66, 39.79, 42.04, 65.75, 71.25; exact mass, *m/z* calcd for $C_{10}H_{16}Cl_2O$ 222.0578, found 222.0576. Anal. Calcd for $C_{10}H_{16}Cl_2O$: C, 53.82; H, 7.23; Cl, 31.78. Found: C, 53.68; H, 7.30; Cl, 32.01.

(1α,5α,6α)-7,7-Dichloro-1,3,3-trimethyl-5-(phenylseleno)bicyclo[4.1.0]-heptane (14c).



[#] The desired product is slowly transformed into a less polar (TLC) compound. It is best to stop the reaction a little short of completion.

Method (a). Phenylselenocyanate (342 mg, 1.88 mmol) in dry THF (1 mL) was added by syringe pump over 1 h to a refluxing solution of dichlorocyclopropane alcohol **14b** (210 mg, 0.94 mmol) and tributylphosphine (0.47 mL, 1.88 mmol) in dry THF (2 mL). After 16 h the mixture was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) using 10% ethyl acetate--hexane gave **14c** (539 mg) contaminated with diphenyl diselenide. This material was dissolved in dry THF-ethanol (4:1) (10 mL) and cooled to -20 °C. Sodium borohydride (100 mg) was added and the mixture was stirred at -20 °C for 10 min. Bromoacetic acid (400 mg) was then added, the cold-bath was removed, and stirring was continued for 30 min. The mixture was then diluted with ether (15 mL) and quenched with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was extracted with ether (1 x 15 mL) and the combined extracts were washed with water (1 x 10 mL) and brine (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm) using 3% ethyl acetate--hexane gave selenide **14c** (282 mg, 82%) as a very slightly yellow solid: FT-IR ($CHCl_3$ cast) 2953, 1580, 1478, 1437, 734, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 3 H), 1.08 (s, 3 H), 1.43 (s, 3 H), 1.44--1.59 (m, 3 H), 1.63 (dd, J = 15.1, 7.3 Hz, 1 H), 1.70 (d, J = 1.4 Hz, 1 H), 3.66 (dm, J = 7.0 Hz, 1 H), 7.32 (m, 3 H), 7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.88, 28.05, 29.33, 30.21, 32.14, 32.76, 33.16, 33.58, 38.58, 40.34, 40.78, 72.74, 128.11, 130.06, 131.82, 133.10; exact mass, m/z calcd for $C_{16}H_{20}Cl_2Se$ 362.0107, found 362.0064. Anal. Calcd for $C_{16}H_{20}Cl_2Se$: C, 53.05; H, 5.57. Found: C, 52.93; H, 5.59.

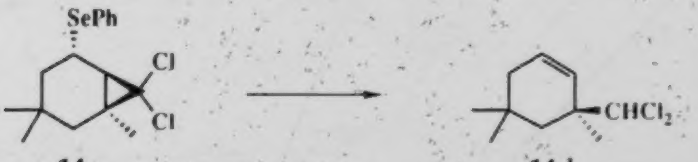
Method (b). (i) (1α,2β,6α)-7,7-Dichloro-4,4,6-trimethylbicyclo-[4.1.0]heptan-2-yl 4-methylbenzenesulfonate. Freshly recrystallised *p*-toluenesulfonyl chloride (2.15 g, 11.25 mmol) and then 4-(dimethylamino)-

pyridine (0.10 g, 0.73 mmol) were added in one portion to a solution of **14b** (2.03 g, 9.18 mmol) in dry pyridine (9 mL). The mixture was stirred at room temperature for 40 h and then concentrated under reduced pressure. The residue was diluted with ethyl acetate (30 mL) and the solution was washed with 1N aqueous hydrochloric acid (2 x 15 mL), saturated aqueous sodium bicarbonate (15 mL), water (10 mL), and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.0 x 17.0 cm) using 8% ethyl acetate--hexane afforded the required tosylate (2.0 g, 57%) as a white solid: FT-IR ($CHCl_3$ cast) 2958, 2931, 2870, 1600, 1362, 1188, 924, 556 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 3 H), 0.92 (s, 3 H), 1.38 (s) and 1.44--1.57 (m) [both signals together correspond to 7 H], 1.75 (d, J = 13.4 Hz, 1 H), 2.46 (s, 3 H), 5.22 (ddd, J = 10.8, 8.8, 7.6 Hz, 1 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.88 (d, J = 8.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.15, 25.57, 26.32, 31.19, 33.24, 33.39, 34.67, 38.90, 40.07, 70.46, 77.39, 128.16, 130.41, 135.30, 145.09; exact mass, *m/z* calcd for $C_{17}H_{22}Cl_2O_3$ 376.0633, found 376.0633. Anal. Calcd for $C_{17}H_{22}Cl_2O_3$: C, 54.11; H, 5.88; Cl, 18.79. Found: C, 54.39; H, 5.82; Cl, 18.53.

The tosylate is rather unstable to silica gel and for larger scale work it is best to crystallise the crude product from cold (0 °C) 1:8 dichloromethane--hexane solution, and to purify material from the mother liquors by chromatography. In this way overall yields of 80 to 90% were obtained. The compound should not be exposed directly to sunlight. When kept in a refrigerator in the dark, no sign of decomposition was observed after 1 month.

(ii) (1α,5α,6α)-7,7-Dichloro-1,3,3-trimethyl-5-(phenylseleno)bicyclo-[4.1.0]heptane (14c). Sodium hydride (0.128 g, 60% in oil, 3.2 mmol) was washed under argon with THF (3 x 2 mL). The residue was then covered with dry tetrahydrofuran (5 mL), and diphenyl diselenide (0.50 g, 1.60 mmol) was added. The mixture was refluxed for 60 min, yielding a light yellow suspension of sodium phenylselenide, which was allowed to cool to room temperature. Dry hexamethylphosphoramide (HMPA) (0.6 mL) was injected with stirring and the solid tosylate (1.15 g, 3,05 mmol) was added to the resulting homogeneous solution. The mixture was refluxed for 18 h, cooled to room temperature and poured into diethyl ether (40 mL). The solution was washed with saturated aqueous sodium bicarbonate (2 x 10 mL), saturated aqueous copper sulfate (10 mL), 1:1 brine--water solution (10 mL), and dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 17 cm) with 5% ethyl acetate--hexane afforded **14c** (1.0 g, 91%) as a slightly yellow oil, containing about 3 mol% of diphenyl diselenide [by ^{1}H-NMR (200 MHz)]. The material can be used directly in the next step.

3-(Dichloromethyl)-3,5,5-trimethylcyclohexene (14d).

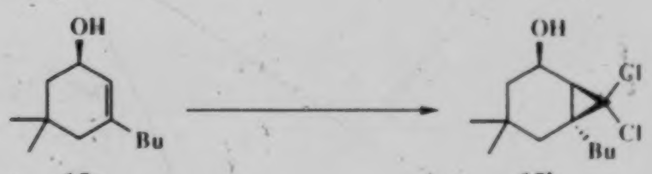


14c **14d**

(a) Photochemical method. The general photochemical method for radical ring opening was followed using triphenyltin hydride (161 μL, 0.63 mmol) and selenide **14c** (208 mg, 0.573 mmol) in dry toluene (3.8 mL). The mixture was stirred and irradiated at -23 °C to -10 °C for 1.5 h and then at -10 °C for 1 h. Carbon tetrachloride (0.5 mL) was added and stirring was continued at 25 °C for 1 h (without irradiation). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm) using hexane gave **14d** (116 mg), contaminated (TLC, silica, 2% ethyl acetate--hexane) by traces of impurity. Kugelrohr distillation of a portion (43.9 mg) of this material gave pure [^{1}H NMR (300 MHz)] **14d** (43.2 mg) as a colorless oil. Corrected yield (that would correspond to distillation of the total product): 114 mg (96%): FT-IR ($CHCl_3$ cast) 2954, 1456, 1365, 1213, 760, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (s,3 H), 1.02 (s, 3 H), 1.28 (s, 3 H), 1.45, (dm, J = 14.2 Hz, 1 H), 1.70 (d, J = 14.2 Hz, 1 H), 1.80 (m, 2 H), 5.53 (dm, J = 10.0 Hz) and 5.55 (s) [both signals together correspond to 2 H], 5.80 (ddd, J = 10.0, 4.9, 3.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.55, 28.18, 30.13, 31.76, 38.46, 44.02, 44.62, 83.33, 128.34, 129.54. Anal. Calcd for $C_{10}H_{16}Cl_2$: C, 57.98; H, 7.79. Found: C, 58.27; H, 7.66.

(b) Thermal method using triethylborane. Triethylborane (1 M in hexane, 5.0 mL, 5.0 mmol) and then triphenyltin hydride (21.93 g, 62.0 mmol) were added dropwise over about 1 min to a cold (-10 °C) and stirred solution of **14c** (18.0 g, 50.0 mmol) in dry hexane (500 mL).[50] After 50 min at -10 °C, carbon tetrachloride (5 mL) was added and the solvents were evaporated. The residue was filtered through a short pad (5 x 7 cm) of silica gel using hexane (500 mL), in order to remove triphenyl(phenylseleno)stannane. The solution was evaporated and Kugelrohr distillation [125-140 °C (27 mm)] of the residue gave **14d** (9.50 g, 92%) as a colorless, homogeneous liquid.

(1α,2β,6α)-6-Butyl-7,7-dichloro-4,4-dimethylbicyclo[4.1.0]heptan-2-ol (15b).

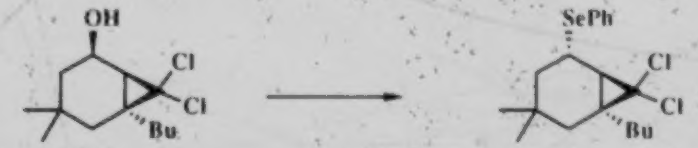


15a

15b

Treatment of 3-butyl-5,5-dimethyl-2-cyclohexen-1-ol[#] (1.3 g, 7.22 mmol) in chloroform (15 mL) with benzyltriethylammonium chloride (36 mg) and aqueous sodium hydroxide 50% w/w (7.1 mL), under identical conditions to those described for **14b**, gave **15b** (1.39 g, 73%) as a white solid: FT-IR ($CHCl_3$ cast) 3400, 2955, 1720, 1486, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s) and 0.93 (t, J = 7.3 Hz, including a singlet at 0.97) [all signals together correspond to 9 H], 1.13--2.0 (m, 12 H), 4.32 (dt, J = 11.5, 7.5 Hz, 1 H); exact mass, m/z calcd for $C_{13}H_{20}Cl_2$ [$(M - H_2O)^+$] 246.0942, found 246.0940.

(1α,5α,6α)-1-Butyl-7,7-dichloro-3,3-dimethyl-5-(phenylseleno)bicyclo-[4.1.0]heptane (15c).



15b **15c**

Addition of phenylselenocyanate (1.46 g, 8.06 mmol) in THF (4 mL) to **15b** (1.06 g, 4.03 mmol) and tributylphosphine (2.0 mL, 8.06 mmol) in THF (9 mL), as described for **14b**, gave **15c** (1.50 g, 92%) as a yellowish oil: FT-IR ($CHCl_3$ cast) 2953, 1598, 1460, 1435, 733, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 6.8 Hz, including a singlet at 0.89, 6 H), 1.05 (s, 3 H), 1.22--1.91 (m, 11 H), 3.65 (ddd, J = 7.1, 2.9, 1.4 Hz, 1 H), 7.24--7.30 (m, 3 H), 7.51--7.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.98, 22.80, 27.55, 27.84, 29.31, 31.53, 32.50, 36.35,

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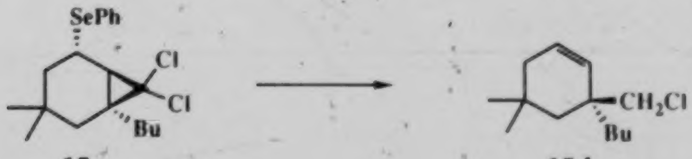
[#] Prepared in 80% yield by conjugate addition (see reference 71) of butyl(phenylthio)copper to 3-bromo-5,5-dimethyl-2-cyclohexen-1-one, followed by reduction to the corresponding allylic alcohol using sodium borohydride and cerium(III) chloride heptahydrate in methanol.

38.06, 39.60, 40.04, 72.04, 127.32, 129.28, 131.12, 133.00; exact mass, *m/z* calcd for $C_{19}H_{26}Cl_2Se$ 404.0577, found 404.0568. Anal. Calcd for $C_{19}H_{26}Cl_2Se$: C, 56.44; H, 6.48. Found: C, 56.68; H, 6.48.

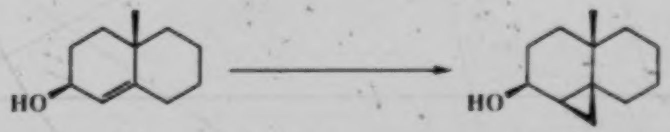
3-Butyl-3-(chloromethyl)-5,5-trimethylcyclohexene (15d).



15c **15d**

Triethylborane (1 M in hexane, 0.7 mL, 0.7 mmol) and then triphenyltin hydride (187 µL, 0.734 mmol) were added dropwise over about 1 min to a cold (0 °C) and stirred solution of **15c** in dry hexane (6 mL).[50] After 45 min at 0 °C, some starting material still remained (TLC control, silica, hexane). A further portion of triphenyltin hydride (60 µL, 0.235 mmol) was added, and stirring was continued for 15 min at 0 °C. At this point, no starting material remained (TLC control), and the mixture contained mainly the dichloride corresponding to the desired ring opening, with traces (<5%) of the monochloride **15d** (VPC, 220 °C). Triphenyltin hydride (250 µL, 0.98 mmol) was added in one portion to the cold (0 °C) solution and the cold-bath was left in place. The mixture was stirred for 14 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 x 21 cm) using hexane afforded the monochloride **15d** (144 mg, 96%) as a colorless liquid: FT-IR ($CHCl_3$ cast) 2953, 1450, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 6.8 Hz, 3 H), 0.96 (s, 6 H), 1.10--1.60 (m, 8 H), 1.80 (dd, J = 4.0, 2.1 Hz, 2 H), 3.46 (s, 2 H), 5.48 (dt, J = 10.2, 1.2 Hz, 1 H), 5.74 (dt, J = 10.2, 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.13, 23.35, 25.66, 29.36, 29.72, 31.05, 38.34, 39.08, 39.61, 43.06, 53.01, 127.31, 130.14. Anal. Calcd for $C_{13}H_{23}Cl$: C, 72.70; H, 10.79. Found: C, 73.12; H, 10.78.

(1aα,2β,4aβ)-Decahydro-4a-methylcyclopropa[d]naphthalen-2-ol (16b).[72]



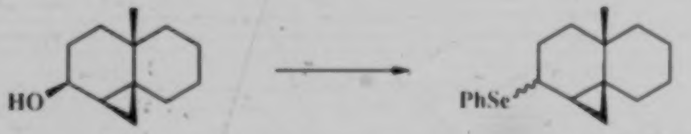
16a **16b**

A mixture of zinc powder (BDH Chemicals, 1.96 g, 30 mmol) and dry DME (10 mL), maintained under a static atmosphere of argon, and contained in a 100-mL round-bottomed flask equipped with a condenser, was sonicated[73] for 20 min at 55 °C. A mixture[72] of alcohols **16a** and **17a** (in a ratio of 87:13, respectively) (500 mg, 3.0 mmol) was then added in one portion, followed by dropwise addition of diiodomethane over 15 min. Sonication was continued and, after a few min, an exothermic reaction began, causing the DME to reflux gently. Sonication was continued for 6 h after the diiodomethane had been added. [This experiment was done several times and, in some instances, heating at reflux for a few hours was necessary in order to complete the reaction.] The mixture was then diluted with ether (30 mL) followed by slow addition of saturated aqueous ammonium chloride (20 mL). The mixture was filtered through a pad of Celite (4.0 x 4.0 cm). The pad was washed with ether (3 X 20 mL) and the combined organic layers were washed with 5% w/v aqueous sodium thiosulfate (1 x 20 mL), water (1 x 20 mL), and brine (1 x 20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) using 20% ethyl acetate--hexane afforded **16b** and **17b** (372 mg, 68%) as a brownish solid, which contained the two isomers in a ratio of 87:13 respectively [^{1}H NMR, (300 MHz)].

A mixture of **16b** and **17b** (87:13, about 2.4 g), obtained from a different experiment, was separated by chromatography over neutral alumina (grade III) (3.5 x 20 cm) using ether--benzene mixtures (2 to 20% ether--benzene). Pure **16b** (1.7 g, 70% of the original mixture) and a mixture of **16b** and **17b** (20:80, respectively; 0.65 g, 30% of the original mixture) were obtained. We later found that the compounds could be separated more conveniently by flash chromatography over silica gel, using 12% ethyl acetate--hexane.

Alcohol **16b** had: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.08 (dd, J = 9.2, 4.7 Hz, 1 H), 0.55 (broad d, J = 13.5 Hz, 1 H), 0.62 (t, J = 4.9 Hz, 1 H), 0.90 (m, 1 H), 1.02 (s, 3 H), 1.10--1.33 (m, 5 H), 1.48--1.79 (m, 6 H), 1.94 (dt, J = 13.0, 3.9 Hz, 1 H), 4.17 (broad t, J = 13.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 10.22, 22.36, 25.52, 25.58, 26.83, 27.46, 28.00, 30.29, 31.10, 34.66, 35.15, 63.85. The VPC retention times at 170 °C were 5.71 and 6.21 min for **16b** and **17b**, respectively.

(1aα,2α,4aβ)- and (1aα,2β,4aβ)-Decahydro-4a-methyl-2-(phenylseleno)-cyclopropa[d]naphthalene (16c).

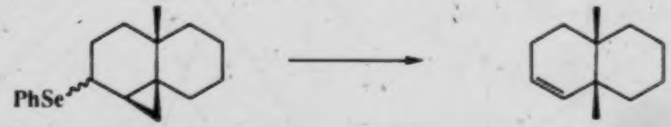


16b **16c**

The general method reported in the literature[43] was followed, but with some modifications. Phenylselenocyanate (511 mg, 2.79 mmol) in dry THF (1 mL) was added over 1 h to a cold (-78 °C), stirred solution of cyclopropyl alcohol **16b** (251 mg, 1.39 mmol) and tributylphosphine (695 μL, 2.79 mmol) in dry THF (4 mL). The cold-bath was left in place and stirring was continued for

12 h, during which time the mixture attained room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm) using 4% ethyl acetate--hexane afforded a yellow oil consisting of **16c** and diphenyl diselenide. This material was dissolved in a mixture of dry THF (8 mL) and absolute ethanol (2 mL), and the solution was cooled to -20 °C. Sodium borohydride (100 mg) was added in one portion. Bubbling was observed and the yellow coloration due to diphenyl diselenide disappeared. Stirring was continued for 5 min at -20 °C, and bromoacetic acid (500 mg) was added in one portion. The cold-bath was removed and the mixture was stirred for 1 h, and diluted with ether (30 mL). The reaction was quenched with saturated aqueous sodium bicarbonate (1 x 15 mL). The aqueous layer was extracted with ether (1 x 30 mL) and the combined organic extracts were washed successively with saturated aqueous sodium bicarbonate (1 x 15 mL), water (1 x 15 mL), and brine (1 x 15 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm) using 0.5% ethyl acetate--hexane afforded a mixture of selenides **16c** (366 mg, 82%) as a colorless oil: FT-IR ($CHCl_3$ cast) 2928, 1580, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.27 (m, 2 H), 0.48 (dm, J = 13.5 Hz, 1 H), 0.99 (s, 3 H), 1.0--1.27(m, 6 H), 1.41--1.81 (m, 7 H), 1.86 (dt, J = 13.9, 3.5 Hz, 1 H), 3.41 (dd, J = 11.0, 7.4 Hz, 1 H), 7.21--7.32 (m, 3 H), 7.53--7.63 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.04, 22.61, 25.57, 25.61, 25.80, 27.43, 27.91, 30.28, 35.32, 35.89, 39.46, 126.95, 128.91, 130.53, 133.81; exact mass, *m*/*z* calcd for $C_{18}H_{24}Se$, 320.1043, found 320.1040. Anal. Calcd for $C_{18}H_{24}Se$: C, 67.70; H, 7.57. Found: C, 68.21; H, 7.55.

Cis-1,2,3,4,4a,5,6,8a-Octahydro-4a,8a-dimethylnaphthalene (16d).



16d **16e**

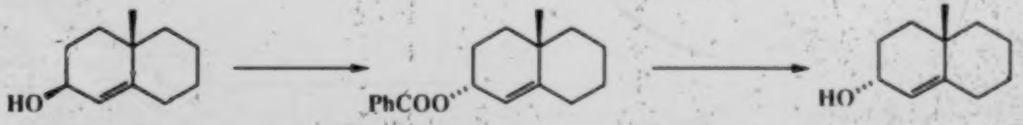
(a) Photochemical method. The general photochemical method for radical ring opening was followed using the selenides **16c** (57 mg, 0.178 mmol) in dry hexane (0.9 mL), and tributyltin hydride (72 µL, 0.267 mmol). The mixture was stirred and irradiated for 2 h at -5 °C to 5 °C, and evaporated. Flash chromatography of the residue over silica gel (1 x 20 cm) using hexane afforded, after careful evaporation of the solvent,# an oil (26.0 mg). Kugelrohr distillation (80 °C, 15 mm) (to effect complete removal of solvent) gave **16d** (25 mg, 84%) as a colorless oil: FT-IR ($CHCl_3$ cast) 2970, 2923, 2859, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3 H), 0.88 (s, about 3 H), 1.05--1.55 (m, 10 H), 2.0 (m, 2 H), 5.28 (dt, J = 10.0, 2.0 Hz, 1 H), 5.51 (dt, J = 10.0, 3.4 Hz, 1 H), 5.55--5.72 [m, 0.12 H (from an olefinic byproduct, which amounted to 6% of the total)]; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 22.20, 22.79, 23.25, 23.33, 33.80, 37.18, 37.48, 124.00, 131.57, 138.15; exact mass, *m/z* calcd for $C_{12}H_{20}$ 164.1565, found 164.1562.

The ^1H NMR spectrum shows that the oil contains the desired material (93%), an olefinic byproduct (6%), and the product of reduction without ring opening (1%). The ^1H NMR chemical shifts of **16d** were identical with those reported for material synthesized[74] by another route. We are not certain if the ^{13}C NMR signals at 124.00 and 131.57 correspond to **16d** or to the olefinic byproduct.

# The evaporation was done at 25 °C under water pump vacuum, and the residual oil was kept under water pump vacuum for a maximum of 2 min.

(b) Thermal method using triethylborane. Tributyltin hydride (328 µL, 1.22 mmol) and then triethylborane (1M in hexanes, 121 µL, 0.121 mmol) were each added in one portion to a cooled (-5 °C) and stirred solution of selenides **16c** in dry hexane (2 mL), and then air (12 mL) was injected into the solution over a period of 2 h (syringe pump). Carbon tetrachloride (0.5 mL) was then injected and the solvent was evaporated. The residue was processed as described above and gave **16d** (58 mg, 85%) as a colorless oil, whose ^{1}H NMR spectrum showed the desired material **16d** (97%), the olefinic byproduct (2%) and product of reduction without ring opening (1%).

2α,3,4,4a,5,6,7,8-Octahydro-4aβ-methyl-2-naphthol (17a).

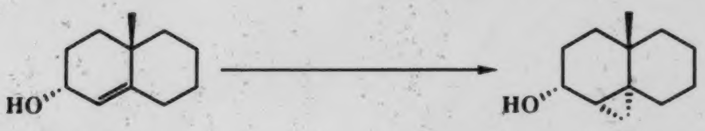


16a:**17a**::87:13 **17a**:**16a**::79:21

(a) 2α-(Benzoyloxy)-2α,3,4,4a,5,6,7,8-Octahydro-4aβ-methylnaphthalene. Triphenylphosphine (4.74 g, 18.08 mmol) and then benzoic acid (2.21 g, 18.08 mmol) were each added in one portion to a magnetically stirred solution of **16a** and **17a** (in a ratio of 87:13, respectively) (1.5 g, 9.04 mmol) in dry THF (70 mL). Diethylazodicarboxylate (2.84 mL, 18.08 mmol) in dry THF (20 mL) was then injected over 30 min (syringe pump). After the addition, the mixture was stirred for 1 h, evaporated, and diluted with dichloromethane (250 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (1 x 100 mL), water (1 x 100 mL), and brine (1 x 100 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (6 x 18 cm) using 25% dichloromethane--hexane afforded a chromatographically inseparable (TLC) mixture of benzoates [in a ratio of 21:79; ^{1}H NMR (200 MHz)] (2.06 g, 82%) as a colorless oil: IR (neat) 2925, 1705, 1270, 1108, 718 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.09 (s, 2.36 H), 1.16 (s, 0.64 H), 1.20--2.13 (m, 13 H), 2.13--2.29 (m, 1 H), 5.35--5.41 (m, 1 H), 5.50--5.56 (m, 1 H), 7.38--7.46 (m, 2 H), 7.50--7.57 (m, 1 H), 8.02--8.09 (m, 2 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) (major isomer) δ 22.11, 22.84, 25.04, 27.88, 32.36, 35.02, 41.74, 68.68, 117.39, 128.23, 129.58, 131.10, 132.61, 151.02, 166.30; (minor isomer) δ 22.28, 23.81, 24.93, 28.42, 37.02, 41.92, 71.46, 119.19, 128.23, 129.58, 130.86, 132.68, 148.76, 166.45.

(b) 2α,3,4,4a,5,6,7,8-Octahydro-4aβ-methyl-2-naphthol (17a). A mixture of the above benzoates (2.07 g, 7.67 mmol) in methanol (80 mL) and 20% w/v aqueous sodium hydroxide (7 mL) was stirred at room temperature for 5 h, quenched with saturated aqueous ammonium chloride (50 mL), and concentrated. The residue was extracted with ether (150 mL) and the organic extract was washed with water (2 x 25 mL), and brine (1 x 25 mL), and dried (MgSO$_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 22 cm) using 20% ethyl acetate--hexane afforded **17a** and **16a** (1.17 g, 92%) as a colorless oil which was a mixture of the isomers [^{1}H NMR (300 MHz)] in a 79:21 ratio, respectively: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.02 (s, 2.49 H), 1.10 (s, 0.51 H), 1.11--2.52 (m, 14 H), 4.02--4.12 (m, 0.87 H), 4.14--4.22 (m, 0.13 H), 5.26--5.31 (m, 0.13 H), 5.42 (d, J = 4.2 Hz, 0.83 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) (major isomer only) δ 22.08, 22.94, 27.90, 32.27, 34.37, 34.99, 41.45, 64.65, 121.46, 148.28.

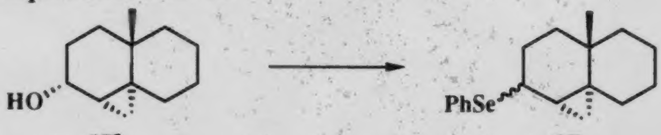
(1aβ,2α,4aβ)-Decahydro-4a-methyl-cyclopropa[d]naphthalen-2-ol (17b).



17a **17b**

The procedure described for **16b** was followed using zinc powder (6.96 g, 107.4 mmol) in dry DME (40 mL), a mixture[75] of **17a** and **16a** (**17a**:**16a**::79:21) (1.78 g, 10.74 mmol), and diiodomethane (3.03 mL, 37.6 mmol), except that, after sonication at 55 °C for 6 h, more zinc powder (1.39 g, 21.4 mmol) and diiodomethane (0.86 mL, 10.74 mmol) were added, followed by refluxing for 30 min, and sonication for 6 h at 55 °C. This modification was necessary to ensure complete reaction. Flash chromatography over silica gel (3 x 20 cm) using 20% ethyl acetate--hexane afforded **17b** and **16b** (1.58 g, 82%) as a mixture of isomers in a 79:21 ratio, respectively [^{1}H NMR (300 MHz)]. The mixture was separated by flash chromatography over silica gel using 12% ethyl acetate--hexane. Alcohol **17b** had: FT-IR ($CHCl_3$ cast) 3375, 2922, 2859, 1484, 1056 cm^{-1} ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.10 (dd, J = 8.6, 4.7 Hz, 1 H), 0.52 (dm, J = 13.2 Hz, 1 H), 0.73 (m, 1 H), 0.99--1.09 (m, including a singlet at 1.03, 4 H), 1.11--1.71 (m, 11 H), 1.88--2.03 (m, 2 H), 4.36 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 10.88, 22.14, 22.22, 25.37, 26.44, 27.30, 30.11, 30.95, 33.01, 33.43, 38.80, 64.61; exact mass, *m/z* calcd for $C_{12}H_{20}O$ 180.1514, found 180.1514.

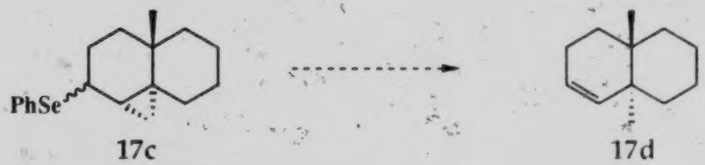
(1aα,2β,4aα)- and (1aα,2α,4aα)-Decahydro-4a-methyl-2-(phenylseleno)-cyclopropa[d]naphthalene (17c).



17b **17c**

The procedure described for selenide **16c** was followed using alcohol **17b** (240 mg, 1.39 mmol) in dry THF (4.5 mL), tributylphosphine (690 µL, 2.78 mmol), and phenylselenocyanate (510 mg, 2.78 mmol) in dry THF (0.5 mL). Diphenyl diselenide was removed as described for **16c**, using sodium borohydride (100 mg) and bromoacetic acid (500 mg). After workup, flash chromatography of the residue over silica gel (2 x 20 cm) using 1% ethyl acetate--hexane afforded a mixture of selenides **17c** (304 mg, 72%) as a slightly yellow oil. The material, which contained the isomers in a ratio of 75:25, based on ^{1}H NMR (300 MHz) signals at δ 3.65 and 4.06, had: FT-IR ($CHCl_3$ cast) 2925, 1580, 1477, 1437, 758, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) (major isomer only) δ 0.21 (dd, J = 9.2, 4.8 Hz, 1 H), 0.43 (m, 2 H), 0.93--1.88 (m, including a singlet at 1.09, 13 H), 1.97 (ddt, J = 8.6, 3.6, 2.1 Hz, 1 H), 3.67 (t, J =9.2 Hz, 1 H), 7.30 (m, 3 H), 7.61 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.79, 21.88, 22.01, 25.26 (two coincident signals), 30.45, 30.85, 33.09, 35.22, 37.68, 38.45, 126.97, 128.91, 130.92, 133.80; exact mass, *m/z* calcd for $C_{18}H_{24}Se$ 320.1043, found 320.1042. Anal. Calcd for $C_{18}H_{24}Se$: C, 67.70; H, 7.57. Found: C, 67.31; 7.51.

Attempted Preparation of *Trans*-1,2,3,4,4a,5,6,8a-Octahydro-4a,8a-dimethylnaphthalene (17d).



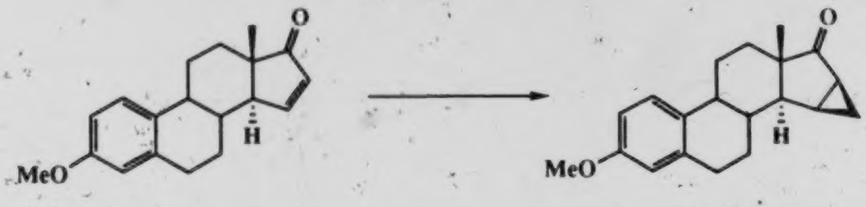
(a) Thermal procedure. The general procedure for thermal radical ring opening was followed using selenides **17c** (60 mg, 0.187 mmol) in benzene (0.5 mL), triphenyltin hydride (72 µL, 0.28 mmol), AIBN (3 mg, 0.02 mmol) and a reaction time of 15 min. Flash chromatography of the crude product over silica gel (1 x 15 cm) using hexane afforded a mixture of hydrocarbons (26.2 mg) containing a compound tentatively identified as **32** [~ 70 mol%, ^{1}H NMR (300 MHz)] as the major component, and unidentified olefinic byproducts: ^{1}H NMR ($CDCl_3$, 300 MHz) (most characteristic peaks of the major component only) δ 0.04 (dd, J = 9.0, 4.5 Hz, 1 H), 0.36--0.45 (m, 2 H), 0.68 (m, 1 H), 1.10 (s, 3 H), 1.93 (m, 2 H); (minor component) δ 5.40 (broad s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major component only) δ 15.12, 15.79, 18.11, 20.29, 21.99, 22.41, 25.59, 33.52, 34.79, 39.40.

(b) Photochemical procedure. The general photochemical method for radical ring opening was followed except that the stannane was added slowly: Triphenyltin hydride (80 μL, 0.234 mmol) in dry THF (0.2 mL) was added over 45 min (syringe pump) to a cold (-70 °C) and stirred solution of **17c** in dry THF (0.2 mL). Stirring and irradiation were continued at -70 °C to -10 °C for 45 min, and then at 0 °C for 45 min. Flash chromatography of the crude product over silica gel (1 x 15 cm) using hexane afforded 23 mg of a mixture of hydrocarbons (23 mg) containing **32** [> 80 mol%, ^{1}H NMR (300 MHz)] as the major component, along with one unidentified olefinic compound.#

The olefinic byproduct from the attemted preparation of **17d** had: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.15--0.24 (m, 1 H), 0.96 (d, J = 6.2 Hz, 3 H), 1.13 (s, 9 H), 1.39--1.47 (m, 1 H), 2.17 (d, J = 16.4 Hz) and 2.24 (t, J = 6.4 Hz) [both signals together correspond to 3 H], 2.45 (dd, J = 16.4, 7.2 Hz, 1 H), 3.67 (tm, J = 7.2 Hz, 2 H), 5.48--5.51 (broad m, 1 H), 7.31--7.48 (m, 6 H), 7.59--7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.27, 19.22, 23.89, 24.49, 26.89, 31.91, 34.07, 38.61, 63.15, 127.62, 128,46, 134.08, 135.61, 139.74.

# No significant change in the product ratio was observed when the addition of the stannane was done at 0 °C instead of -70 °C.

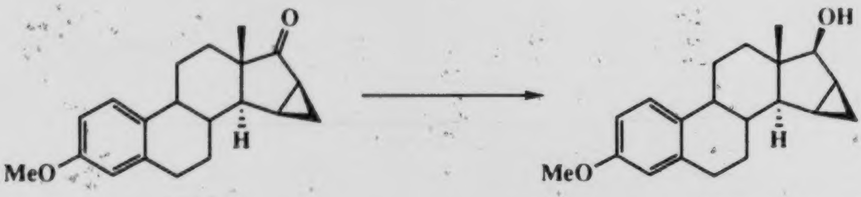
(15α,16α)-15,16-Dihydro-3-methoxy-3'*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraen-17-one (18b).



18a **18b**

Treatment of the pure unsaturated ketone **18a** with trimethylsulfoxonium iodide and sodium hydride according to the literature method,[76] followed by flash chromatography over silica gel using 20% ethyl acetate--hexane, gave the cyclopropane **18b** (72%): FT-IR (CH_2Cl_2 cast) 2948, 1710, 1611, 1498, 1282, 1253, 1043, 889 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.0 (s, 3 H), 1.17 (m, 1 H), 1.45--1.88 (m, 8 H), 2.05 (m, 1 H), 2.13--2.24 (m, 2 H), 2.24--2.43 (m, 2 H), 2.96 (m, 2 H), 3.78 (s, 3 H), 6.66 (d, J = 2.8 Hz, 1 H), 6.71 (dd, J = 8.5, 2.8 Hz, 1 H), 7.17 (d, J = 8.5 Hz, 1 H); exact mass, *m/z* calcd for $C_{20}H_{24}O_2$ 296.1777, found 296.1776.

(15α,16α,17β)-15,16-Dihydro-3-methoxy-3'*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraen-17-ol (18c).

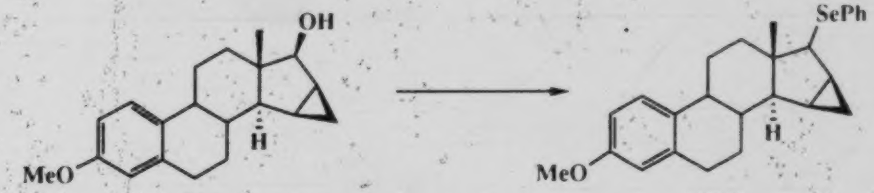


18b **18c**

Treatment of the cyclopropyl ketone with lithium aluminum hydride according to the literature method,[76] followed by flash chromatography over silica gel using 30% ethyl acetate- hexane gave pure cyclopropyl alcohol **18c**

(90%): ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.3 (dd, J = 14.0, 8.3 Hz, 1 H), 0.82, (s, 3 H), 0.98 (m, 1 H), 1.17--1.65 (m, 8 H), 1.73--1.89 (m, 2 H), 2.07--2.37 (m, 3 H), 2.92 (m, 2 H), 3.78 (s, 3 H), 4.10 (m, 1 H), 6.65 (d, J = 3.2 Hz) and 6.72 (dd, J = 8.4, 3.2 Hz) [both signals together correspond to 2 H], 7.18 (d, J = 8.4 Hz, 1 H).

(15α,16α)-15,16-Dihydro-3-methoxy-17-(phenylseleno)-3'*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraene (18d).#



18c **18d**

Tributylphosphine (83 μL, 0.334 mmol) was added dropwise over 1 min to a stirred solution of phenylselenocyanate(61 mg, 0.334 mmol) and cyclopropyl alcohol **18c**[76] (50 mg, 0.167 mmol) in dry THF (0.6 mL). Stirring was continued for 4 h and another portion of phenylselenocyanate (30 mg, 0.16 mmol) and of tributylphosphine (42 μL, 0.0.16 mmol) were added. The mixture was stirred for 12 h at room temperature and was then diluted with dichloromethane (20 mL) and water (5 mL). The organic layer was washed with brine (1 x 5 mL), and dried (MgSO$_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.2 x 15 cm) using 30% dichloromethane--hexane gave **18d** (59 mg, 80%) as a gummy solid free of diphenyl diselenide: FT-IR (CHCl$_3$ cast) 2920, 1605, 1578, 1500, 1255, 1039,737 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.35 (dd, J = 14.0, 8.2 Hz, 1 H), 0.95 (m, including a singlet at 1.0, 4 H), 1.38--1.72 (m, 6 H), 1.90 (dt, J = 12.5, 3.2 Hz, 1 H),

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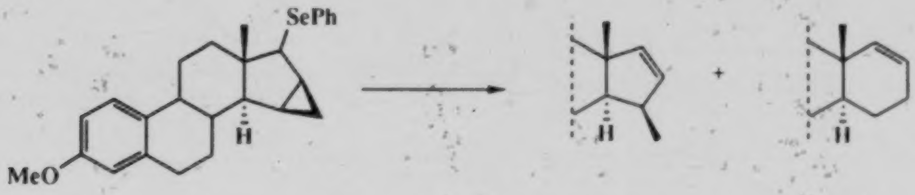
# Stereochemistry at C(17) was not determined

2.03–2.38 (m, 4 H), 2.93 (m, 2 H), 4.78 (s, 1 H), 7.66 (d, J = 3.2 Hz) and 7.71 (dd, J = 8.4, 3.2 Hz) [both signals together correspond to 2 H], 7.16 (d, J = 8.4 Hz, 1 H), 7.28 (m, 3 H), 7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.03, 18.31, 20.88, 26.74, 26.85, 28.55, 29.76, 37.43, 41.25, 41.91, 44.08, 52.39, 55.19, 57.61, 11.35, 113.86, 125.95, 126.68, 128.97, 131.26, 132.76, 133.28, 137.90, 157.50; exact mass, *m/z* calcd for $C_{26}H_{30}OSe$ 438.1462, found 438.1459. Anal. Calcd for $C_{26}H_{30}OSe$: C, 71.38; H, 6.91; O, 3.66. Found: C, 71.53; H,6.88; O, 3.69.

In a similar experiment, done on a larger scale (593 mg of starting material), the selenide was obtained in 75% yield.

(15β)-3-Methoxy-15-methylestra-1,3,5(10),16-tetraene (18e).



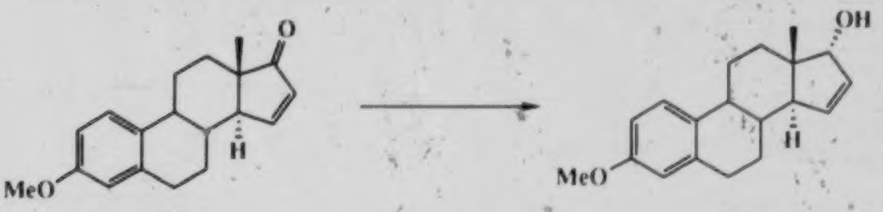
18d **18e** **18f**

The general photochemical method for radical ring opening was followed using cyclopropyl selenide **18d** (275 mg, 0,981 mmol) in toluene (5.0 mL) and tributyltin hydride (396 μL, 1.47 mmol). The mixture was stirred and irradiated for 2.5 h at 0 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 15 cm) using 20% dichloromethane--hexane gave **18e** (167 mg, 94%; 79% after correction for the fact that the material is contaminated [^{1}H NMR (200 MHz)] with 16 mol% of the ring expansion product **18f** as a white semi-solid: FT-IR ($CHCl_3$ cast) 3033, 1610, 1575, 1500, 1256, 1237, 1042, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 0.6 H), 0.99 (s) and 1.01 (d, J = 7.2 Hz) [both signals together correspond to 4.8

H], 1.15--1.38 (m, 0.9 H), 1.40--1.92 (m, 5.8 H), 2.08 (m, 1.4 H), 2.28 (m, 2 H), 2.65 (dd of quintets, J = 7.2, 2.9, 1.1 Hz, 0.83 H), 2.80--3.02 (m, 2 H), 3.76 (s, 3 H), 5.50 (s, 0.34 H), 5.77 (dd, J = 5.9, 3.0 Hz, 0.83 H), 5.87 (dd, J = 5.9, 1.5 Hz, 0.83 H), 6.67 (d, J = 3.2 Hz) and 6.70 (dd, J = 8.4, 3.2 Hz) [both signals together correspond to 2 H], 7.19 (d, J = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major isomer) δ 14.90, 22.87, 26.17, 27.67, 29.68, 35.50, 37.86, 39.06, 45.17, 46.41, 55.17, 56.04, 111.20, 113.85, 125.69, 133.50, 135.28, 138.00, 142.08, 157.48; (minor isomer) δ 20.00, 20.22, 26.25, 26.36, 26.42, 30.16, 34.72, 38.55, 44.08, 47.36, 111.49, 113.49, 123.69, 126.15, 133.23, 139.50, 157.47; exact mass, *m/z* calcd for $C_{20}H_{26}O$ 282.1984, found 282.1977.

The results were slightly different when the reaction was done with triphenyltin hydride at -30 °C (16% ring expansion) or in refluxing benzene (with triphenyltin hydride) (22% ring expansion).

(17α)-3-Methoxyestra-1,3,5(10),15-tetraen-17-ol (19b).



19a **19b**

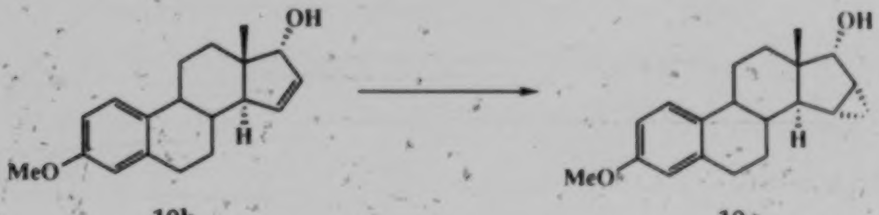
(a) (17β)-3-Methoxyestra-1,3,5(10),15-tetraen-17-ol.

Cerium(III) chloride heptahydrate[77] (1.58 g, 4.25 mmol) was added in one portion to a cooled (-23 °C) and stirred suspension of **19a** (0.98 g, 3.54 mmol) in dry methanol (18 mL) and dry THF (4 mL). Sodium borohydride (161 mg, 4.25 mmol) was then added in portions over 5 min. Stirring was continued for 30 min at -23 °C. The cold-bath was replaced by an ice bath and, after 30 min, this was removed. Stirring was continued for an additional 45 min. The mixture was diluted with dichloromethane (20 mL) and quenched with saturated aqueous ammonium chloride (10 mL). The aqueous layer was extracted with dichloromethane (1 x 20 mL) and the combined organic extracts were washed with water (1 x 10 mL), and brine (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm) using 5% ethyl acetate--dichloromethane gave the desired alcohol[76] (969 mg, 98%) as a white solid: FT-IR ($CHCl_3$ cast) 3460, 2927, 1605, 1502, 1237, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3 H), 1.40--1.51 (m, 1 H), 1.53--1.73 (m, 4 H), 1.98--2.13 (m,3 H), 2.23--2.39 (m, 2 H), 2.91 (m, 2 H), 3.78 (s, 3 H), 4.41 (broad s, 1 H), 5.73 (ddd, J = 5.9, 3.1, 1.3 Hz, 1 H), 6.04 (broad d, J = 5.9 Hz, 1 H), 6.65 (d, J = 2.5 Hz, 1 H), 6.72 (dd, J = 8.5, 2.5 Hz, 1 H), 7.21 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.24, 26.14, 27.64, 29.63, 34.74, 36.42, 44.43, 51.36, 55.24, 56.76, 85.72, 111.50, 113.92, 126.13, 131.61, 132.58, 134.68, 137.87, 157.57; exact mass, *m/z* calcd for $C_{19}H_{24}O_2$ 284.1777, found 284.1778.

(b) (17α)-3-Methoxyestra-1,3,5(10),15-tetraen-17-yl benzoate. Triphenylphosphine (1.74 g, 6.6 mmol) and benzoic acid (806 mg, 6.6 mmol) were added successively to a magnetically stirred solution of the above alcohol (940 mg, 3.31 mmol) in dry THF (27 mL). Diethyl azodicarboxylate (1.04 mL, 6.6 mmol) in dry THF (6 mL) was then added dropwise over 30 min and stirring was continued for 2 h.[78] At this point, the reaction was still incomplete (TLC control, silica, 30% ethyl acetate--hexane). Further portions of triphenylphosphine (1.74 g, 6.6 mmol), benzoic acid (806 mg, 6.6 mmol) and diethyl azodicarboxylate (1.04 mL, 6.6 mmol) were then added and, after an additional 1 h the solvent was evaporated and the residue was taken up in dichloromethane (150 mL). The solution was washed with saturated aqueous sodium bicarbonate (1 x 50 mL), water (1 x 50 mL), and brine (1 x 50 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (4 x 20 cm) using 25 % ethyl acetate--hexane gave the desired benzoate (1.10 g, 86%) as a gummy solid which contained slight impurities (TLC): FT-IR ($CHCl_3$ cast) 2920, 1713, 1500, 1270, 1256, 705 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (s, 3 H), 1.20--2.03 (m, 5 H), 2.13 (m, 1 H), 2.35 (m, 1 H), 2.69 (ddd, J = 11.5, 3.3, 1.7 Hz, 1 H), 2.92 (m, 2 H), 3.77 (s, 3 H), 5.39 (d, J = 2.6 Hz, 1 H), 6.08 (quintet, J = 3.0 Hz, 1 H), 6.39 (dd, J = 5.9, 1.3 Hz, 1 H), 6.65 (d, J =2.2 Hz, 1 H), 6.72 (dd, J = 2.2 Hz, 1 H), 7.21 (d, J = 8.5 Hz, 1 H), 7.43 (m, 2 H), 7.53 (m, 2 H), 8.05 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.24, 25.75, 28.16, 29.60, 31.06, 36.09, 44.41, 46.24, 55.21, 56.14, 84.57, 111.52, 113.90, 126.09, 128.36, 129.61, 129.78, 130.79, 132.50, 132.80, 137.78, 139.58, 157.60, 166.47; exact mass, *m*/*z* calcd for $C_{26}H_{28}O_3$ 388.2038, found 388.2033.

(c) (17α)-3-Methoxyestra-1,3,5(10),15-tetraen-17-ol (19b).[79] Methanol (21 mL) and 20% w/v aqueous sodium hydroxide (9 mL) were added to a magnetically stirred solution of the above benzoate (1.06 g, 2.73 mmol) in THF (7 mL). Stirring was continued for 16 h and the mixture was then quenched with saturated aqueous ammonium chloride (15 mL). Most of the THF was evaporated (water pump vacuum) and the residue was extracted with dichloromethane (1 x 100 mL). The organic phase was washed with water (2 x 20 mL), and brine (1 x 20 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm) afforded **19b** (592 mg, 76%) as a white solid: FT-IR ($CHCl_3$ cast) 3300, 2929, 1610, 1501, 1258, 1046, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (s, 3 H), 1.42--1.75 (m, 5 H), 1.96 (m, 1 H), 2.10 (m, 1 H), 2.28 (dt, J = 10.5, 4.4 Hz, 1 H), 2.36--2.53 (m, 2 H), 2.90 (m, 2 H), 3.78 (s, 3 H), 4.15 (broad d, J = 2.0 Hz, 1 H), 6.0 (m, 1 H), 6.22 (dd, J = 4.2, 1.4 Hz, 1 H), 6.63 (d, J = 2.8 Hz, 1 H), 6.72 (dd, J = 8.5, 2.8 Hz, 1 H), 7.21 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.50, 25.75, 28.19, 29.58, 30.56, 36.04, 44.46, 46.15, 54.80, 55.20, 82.47, 111.45, 113.89, 126.06, 132.68, 133.19, 137.20, 137.79, 157.50; exact mass, *m*/*z* calcd for $C_{19}H_{24}O_2$ 284.1777, found 284.1777. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.95; H, 8.52.

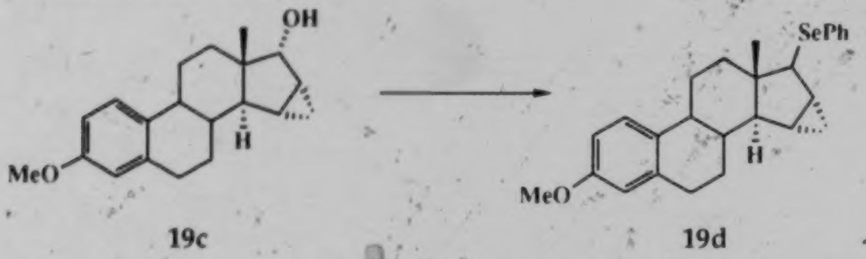
(15β,16β,17α)-15,16-Dihydro-3-methoxy-3'*H*-cycloprop[15,16]estra-1,3,5(10),15-tetraen-17-ol (19c).



19b **19c**

The procedure is based on a literature method.[80] Allylic alcohol **19b** (200 mg, 0.7 mmol) and then dry ether (5 mL) were added to a suspension of zinc-copper couple (436 mg, 6.7 mmol)[81] in dry DME (5 mL) maintained under a static atmosphere of argon in a 25-mL round-bottom-flask equipped with a condenser. Diiodomethane (324 μL, 4.02 mmol) was then added dropwise and the mixture was stirred at reflux temperature (oil bath at 60 °C) for 18 h. At this point the reaction was still incomplete (TLC, silica, 30% ethyl acetate--hexane). Zinc-copper couple (218 mg, 3.3 mmol) and then diiodomethane (162 μL, 2.01 mmol) were added and the mixture was stirred at reflux temperature for an additional 18 h. Saturated aqueous ammonium chloride (10 mL) was added followed by ethyl acetate (10 mL). The resulting slurry was filtered through a pad of Celite (2.0 x 2.0 cm) and the pad was washed with ethyl acetate (5 x 6 mL). The organic filtrate was washed with water (1 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL), water (1 x 10 mL), and brine (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20.0 cm) using 20% ethyl acetate--hexane afforded **19c** (171 mg, 81%; 86% based on conversion) and starting material **19b** (11 mg). Compound **19c** had: FT-IR ($CHCl_3$ cast) 3440, 1600, 1570, 1255, 1230, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.9--1.08 (m, including a singlet at 0.95, 6 H), 1.20--1.80 (m, 8 H), 2.13 (m, 2 H), 2.28 (m, 1 H), 2.88 (m, 1 H), 3.77 (s, 3 H), 3.96 (d, J = 5,5 Hz, 1 H), 6.64 (d, J = 2.8 Hz, 1 H), 6.70 (dd, J = 8.5, 2.8 Hz, 1 H), 7.20 (d, J = 8.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.31, 19.32, 21.12, 25.32, 25.85, 28.78, 29.92, 30.47, 37.98, 43.96, 54.66, 55.21, 56.14, 77.99, 111.41, 113.88, 126.24, 132.78, 138.12, 157.45, 180.97; exact mass, *m/z* calcd for $C_{20}H_{26}O_2$ 298.1933, found 298.1933. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.26; H, 8.94.

(15β,16β)-15,16-Dihydro-3-methoxy-17-(phenylseleno)-3'*H*-cyclopropl[15,16]estra-1,3,5(10),15-tetraene (19d).[#]



Tributylphosphine (0.41 mL, 334 mg, 1.65 mmol) was added to a stirred solution of **19c** (214 mg, 0.72 mmol) in dry THF (4 mL) at 50 °C contained in a 10-mL round-bottomed flask equipped with a condenser. Phenylselenocyanate (303 mg, 1.65 mmol) in dry THF (0.8 mL) was then added over 3 h

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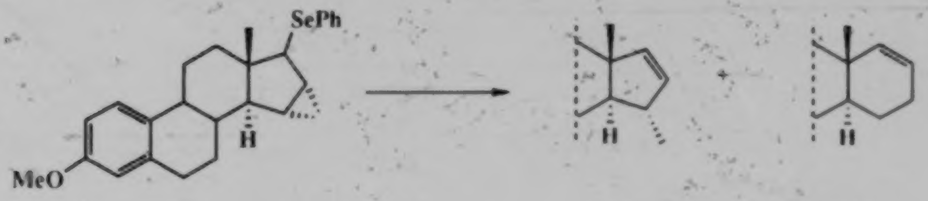
[#] Stereochemistry at C(17) was not determined.

(syringe pump) via the condenser, and stirring was continued for 12 h. The mixture was allowed to cool to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 20.0 cm) using 25% dichloromethane--hexane gave **19d** (197 mg, 63%) as a viscous oil: FT-IR ($CHCl_3$ cast) 2930, 1620, 1590, 1500, 1260, 1050, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.63 (dd, J = 7.8, 3.7 Hz, 1 H), 0.82 (dd, J = 11.0, 5.1 Hz, 1 H), 1.12 (s, 3 H), 1.2--1.93 (m, 8 H), 2.21 (m, 3 H), 2.75 (d, J = 4.8 Hz, 1 H), 2.91 (m, 2 H), 3.80 (s, 3 H), 6.67 (d, J = 2.8 Hz, 1 H), 6.73 (dd, J = 8.5, 2.8 Hz, 1 H), 7.11--7.32 [m, including a doublet at 7.20 (J = 8.5 Hz), 4 H], 7.60 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major peaks only) δ 17.20, 20.74, 26.02, 27.15, 27.25, 28.54, 29.81, 35.63, 38.21, 44.34, 55.13, 57.34, 57.91, 60.16, 111.40, 113.85, 126.16, 128.90, 132.04, 132.13, 132.52, 138.03, 157.52; exact mass, *m/z* calcd for $C_{26}H_{30}OSe$ 438.1462, found 438.1460. Anal. Calcd for $C_{26}H_{30}OSe$: C, 71.38; H, 6.91; O, 3.66. Found: C, 71.28; H, 6.92; O, 3.95.

(15α)-3-Methoxy-15-methylestra-1,3,5(10),16-tetraene (19e).

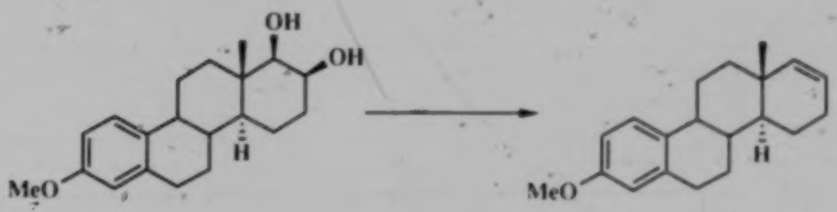


19d **19e** **19f**

The general photochemical method for radical ring opening was followed using tributyltin hydride (110 µL, 0.411 mmol), which was added to a cold (0 °C) solution of **19d** (115 mg, 0.262 mmol) in dry toluene (2.8 mL). The mixture was stirred and irradiated at 0-20 °C for 3 h. At this point, the reaction was still incomplete (TLC control, silica, 5% ethyl acetate--hexane).

Tributyltin hydride (44 µL, 0.164 mmol) was added at 0 °C and the mixture was stirred and irradiated at 0-25 °C for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) using 20% dichloromethane--hexane gave a mixture of **19e** and **19f** in a ratio [^{1}H NMR (300 MHz)] of 84:16, respectively (64 mg, 86%): FT-IR ($CHCl_3$ cast) 2928, 1610, 1575, 1501, 1256, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 0.83 (s, 2.6 H), 0.90 (s, 0.4 H), 1.10--1.42 [m, including a doublet at 1.17 (J = 7.1 Hz), 4 H], 1.42--1.95 (m, 5 H), 2.12 (dm, J = 12.5 Hz, 1.72 H), 2.32 (m, 3 H), 2.57 (quintet, J = 7.5 Hz, 0.86 H), 2.78--3.01 [m, including a doublet at 2.88 (J = 6.5 Hz), 2 H], 3.78 (s, 3 H), 5.45 (d, J = 5.5 Hz, 0.86 H), 5.50 (broad s, 0.28 H), 5.81 (dd, J =5.5, 2.2 Hz, 0.86 H), 6.62 (d, J =2.9 Hz, 1 H), 6.71 (dd, J = 8.6, 2.9 Hz, 1 H), 7.13--7.26 [m, including a doublet at 7.19 (J = 8.6 Hz)], 1 H] ^{13}C NMR ($CDCl_3$, 75.5 MHz) (major isomer) δ 18.97, 20.48, 27.24, 28.58, 30.04, 36.38, 38.43, 39.86, 44.91, 47.97, 55.21, 62.85, 111.55, 113.67, 126.37, 133.00, 136.72, 137.76, 141.53, 157.41; (minor isomer) δ. 20.04, 20.25, 26.26, 26.44, 30.21, 34.76, 38.59, 39.14, 44.12, 47.40, 113.53, 123.94, 126.21, 139.54; exact mass, *m/z* calcd for $C_{20}H_{26}O$ 282.1982, found 282.1978. Anal. Calcd for $C_{20}H_{26}0$: C, 85.05; H, 9.21. Found: C, 85.03; H, 9.44.

3-Methoxy-D-homoestra-1,3,5(10),17-tetraene (18f=19f).[53]



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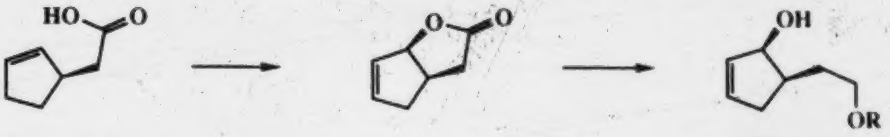
19f

Freshly prepared potassium graphite (C_8K) (3.98 g, 29.4 mmol) and titanium trichloride (2.18 g, 14.19 mmol) were weighed under argon in a glove box and transferred successively to a 250-mL round-bottomed flask equipped with a condenser and containing dry diglyme (60 mL). The mixture was stirred at 85 °C for 2 h under argon. 3-Methoxy-D-homoestra-1,3,5(10)-triene-17α,17aβ-diol **30**[54] (267 mg, 0.84 mmol) was added via the condenser in one portion into the stirred slurry of titanium reagent, and the inside of the condenser was rinsed with dry diglyme (5 mL). Stirring was continued at 150 °C for an arbitrary period of 36 h. The mixture was cooled to room temperature and filtered under a blanket of argon through a pad of Florisil (11 x 4 cm) contained in a sintered funnel equipped with an argon inlet near the top. The column was washed with dichloromethane (400 mL) and ether (200 mL). Evaporation of the filtrate, removal of diglyme by Kugelrohr distillation (80 °C, 3 mm) and flash chromatography of the residue over silica gel (2.5 x 20.0 cm) using 5% ethyl acetate--hexane gave **18f** (219 mg, 92%) as a white solid: FT-IR ($CHCl_3$ cast) 2925, 1600, 1500, 1218, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82--0.98 (m, including a singlet at 0.91, 4 H), 1.20--1.69 (m, 10 H), 1.81--1.95 (m, 1 H), 2.0--2.22 (m, 3 H), 2.22--2.39 (m, 2 H), 2.82--2.93 (m, 2 H), 3.79 (s, 3 H), 5.51 (broad singlet, 2 H), 6.64 (d, J = 2.8 Hz, 1 H), 6.72 (dd, J = 8.4, 2.8 Hz, 1 H), 7.22 (d, J = 8.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.04, 20.15, 26.26, 26.38, 29.74, 30.21, 34.77, 38.60, 39.14, 44.13, 47.41, 55.24, 111.54, 113.53, 123.94, 126,21, 133.30, 138.05, 139.54, 157.48; exact mass, *m/z* calcd for $C_{20}H_{26}O$ 282.1984, found 282.1983. Anal. Calcd for $C_{20}H_{26}O$: C, 85.05; H, 9.28. Found: C, 84.99; H, 9.63.

***Cis*-5-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2-cyclopenten-1-ol (20a).**



20a

(a) *Cis*-(3,3a,4,6a)-Tetrahydro-2*H*-cyclopenta[b]-furan-2-one. Sodium bicarbonate (66.4 g, 0.70 mol) and iodine (120.7 g, 0.47 mol) were added with vigorous stirring to a cooled (0 °C) solution of 2-cyclopentene-1-acetic acid (20.0 g, 0.158 mol) in 75% THF-water. The cold-bath was left in place and allowed to attain room temperature. After 16 h, the reaction mixture was diluted with ether (1000 mL) and washed with water (1 x 250 mL). The organic layer was washed with 10% aqueous sodium thiosulfate (1 x 200 mL), water, (1 x 200 mL), and brine (1 x 200 mL), and dried ($MgSO_4$). Evaporation of the solvent gave the desired iodo lactone (38.4 g) as a red-brown oil, which was used without further purification.

1,8-Diazabicyclo[5.4.0]undec-7-ene (27.8 mL, 0.185 mol) was added in one portion to a stirred solution of the crude iodo lactone (36.12 g, 0.143 mol) in dry benzene (650 mL). The mixture was stirred and refluxed for 4 h, cooled to room temperature, and filtered through a sintered glass funnel to remove insoluble salts. The filtrate was diluted with ether (1000 mL), washed with water (1 x 250 mL), and brine (1 x 250 mL), and dried ($MgSO_4$). Evaporation of the solvent gave crude *cis*-(3,3a,4,6a)-tetrahydro-2*H*-cyclopenta[b]furan-2-one (12.7 g, 71.3%). The combined aqueous layers were saturated with sodium chloride and continuously extracted with ether for 4 h. The ether was dried and evaporated to afford more product (7.2 g, 40.4%): ^1H NMR ($CDCl_3$, 80

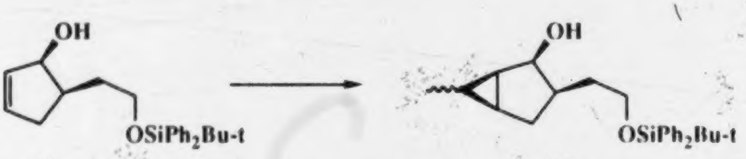
MHz) δ 1.90--3.40 (m, 7 H), 5.40 (d, J = 7.0 Hz, 1 H), 5.50--5.90 (m, 1 H), 5.90--6.20 (m, 1 H). The material was used directly in the next step.

(b) *Cis*-5-(2-Hydroxyethyl)-2-cyclopenten-1-ol. The crude lactone from the previous step (10.0 g, 0.08 mol) was added over 5 min to a cold (0 °C) and stirred suspension of lithium aluminum hydride (6.11 g, 0.161 mol) in ether (300 mL). The cold-bath was removed and stirring was continued for 2 h. The mixture was then quenched by slow addition of saturated aqueous ammonium chloride (200 mL). The organic layer was separated, and the aqueous layer was saturated with sodium chloride and extracted continuously with ether for 16 h. The combined organic extracts were dried ($MgSO_4$) and evaporated to afford the required diol (10.0 g). Flash chromatography over silica gel (7 x 30 cm) using 50% ethyl acetate--hexane gave the pure diol (8.6 g, 86% based on 2-cyclopentene-1-acetic acid): ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.30--2.50 (m, 5 H), 3.0--3.95 (m, 4 H), 4.65 (broad s, 1 H), 5.75--6.15 (m, 2 H).

(c) *Cis*-5-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-2-cyclopenten-1-ol (20a). Imidazole (233 mg, 3.43 mmol) and *tert*-butylchlorodiphenylsilane[82] (440 μL, 1.72 mmol) were added to a cold (0 °C) and stirred solution of the above diol (200 mg, 1.56 mmol) in dry DMF (3.2 mL). The cold-bath was left in place and allowed to attain room temperature. After 11 h, the mixture was quenched by addition of saturated aqueous ammonium chloride (5 mL), and diluted with ether (25 mL). The organic layer was washed with water (1 x 10 mL), and brine (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2.0 x 18.0 cm) using 15% ethyl acetate--hexane gave **20a** (442 mg, 77%) as a thick, colorless oil: FT-IR ($CHCl_3$ cast) 3400, 2930, 2857, 1472, 1427, 1112, 1084, 701, 505 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9 H), 1.68 (ddd, J = 14.4, 9.5, 4.4 Hz, 1 H), 1.96--2.30 (m, 3 H), 2.38 (dddd, J = 15.6, 7.4, 2.8, 1.6

Hz, 1 H), 2.81 (d, J = 4.1 Hz, 1 H), 3.67 (dt, J = 9.7, 3.9 Hz, 1 H), 3.81 (m, 1 H), 4.72--4.81 (broad m, 1 H), 5.92 (m, 1 H), 6.01 (broad dt, J = 6.0, 2.2 Hz, 1 H), 7.32--7.49 (m, 6 H), 7.60--7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.05, 26.82, 31.58, 37.54, 41.63, 64.36, 76.32, 127.77, 129.79, 132.82, 133.08, 133.17, 135.29, 135.60; exact mass, *m*/*z* calcd for $C_{19}H_{21}O_2Si$ [$(M - C_4H_9)^+$] 309.1311, found 309.1311. Anal. Calcd for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25. Found: C, 75.27; H, 8.39.

(1α,2β,3β,5α,6α)- and (1α,2β,3β,5α,6β)-3-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-6-methylbicyclo[3.1.0]hexan-2-ol (20b).[#]



20a **20b**

The procedure is based on a general literature method.[33] Samarium metal (Research Chemicals, Phoenix, Arizona, *ca* 40 mesh, 1.15 g, 7.65 mmol) was flame dried in a 50-mL round-bottomed flask equipped with a Teflon-coated stirring bar and purged with a stream of argon. The flask was allowed to cool to room temperature and dry THF (18 mL) was added, followed by a solution of mercuric chloride in THF (1.5 M, 407 μL, 0.6 mmol). Stirring was continued for 10 min at room temperature and then allylic alcohol **20a** (650 mg, 1.77 mmol) in dry THF (2 mL) was introduced via a cannula over about 10 min. The mixture was cooled to -78 °C and 1,1-diiodoethane (2.0 g, 7.08 mmol) was injected dropwise over about 5 min. The cold-bath was left in

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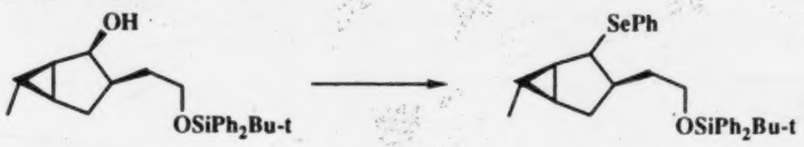
[#] The samarium-mediated cycloprapanation proceeds with syn direction by the hydroxyl (reference 33). The stereochemistry at C(6) was not determined.

place and allowed to attain room temperature. After 8 h, the mixture was diluted with dichloromethane (20 mL) and quenched with saturated aqueous ammonium chloride (15 mL). Stirring was continued for 3 min, and the aqueous layer was separated and extracted with dichloromethane (1 x 25 mL). The combined organic extracts were washed with water (1 x 15 mL), and brine (1 x 15 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm) with 15% ethyl acetate--hexane afforded **20b** (313 mg, 45%; 69% based on conversion) and recovered starting material **20a** (230 mg). Compound **20b** had: FT-IR ($CHCl_3$ cast) 3460, 2929, 2858, 1595, 1428, 1112, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.0 (s, 3 H), 1.0--1.1 (m, including a singlet at 1.05, 11 H), 1.17--1.27 (m, 1 H), 1.32 (ddd, J = 14.3, 9.5, 4.5 Hz, 1 H), 1.42 (m, 1 H), 1.88 (m, 1 H), 2.06 (ddd, J = 13.0, 9.2, 6.3 Hz, 1 H), 2.21 (m, 1 H), 2.70 (broad s, 1 H), 3.54 (dt, J = 10.0, 4.0 Hz, 1 H), 3.67 (dt, J = 10.0, 4.0 Hz, 1 H), 4.63 (broad t, J = 6.5 Hz, 1 H), 3.67 (dt, J = 10.0, 4.0 Hz, 1 H), 7.35--7.48 (m, 6 H), 7.63--7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.08, 19.02, 19.57, 26.83, 26.92, 32.35, 34.61, 35.49, 48.77, 64.66, 73.95, 127.75, 129.75, 133.10, 133.20, 135.58, 135.63; exact mass, *m/z* calcd for $C_{21}H_{25}O_2Si$ [$(M - C_4H_9)^+$] 337.1624, found 337.1622. Anal. Calcd for $C_{25}H_{34}O_2Si$: C, 76.09; H, 8.68. Found: C, 75.77; H, 8.58.

(1,1-Dimethylethyl)[2-[6-methyl-2-(phenylseleno)-bicyclo[3.1.0]hex-3-yl]ethoxy]diphenylsilane (20c).[#]

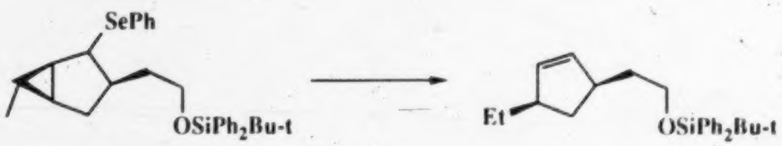


20b **20c**

[#] Stereochemistry at C(2) and C(6) was not determined.

Phenylselenocyanate (137 mg, 0.75 mmol) in dry THF (0.5 mL) was added dropwise over about 5 min to a stirred solution of cyclopropyl alcohol **20b** (197 mg, 0.5 mmol) and tributylphosphine (187 µL, 0.75 mmol) in dry THF (5 mL). Stirring at room temperature was continued for 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm) using 20% dichloromethane--hexane (to remove diphenyl diselenide) followed by 5% ethyl acetate--hexane gave the selenide **20c** as a single isomer (154 mg, 58 %) and an olefinic byproduct (48 mg, 26 %). Selenide **20c** had: FT-IR ($CHCl_3$ cast) 2929, 1580, 1111, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.52 (d of septets, J = 6.0, 3.2 Hz, 1 H), 0.91 (d, J = 6.0 Hz, 3 H), 1.02 (s, 9 H), 1.06--1.50 (m, 5 H), 1.52 (m, 1 H), 2.14 (ddd, J = 13.0, 9.7, 5.5 Hz, 1 H), 2.33 (m, 1 H), 3.27 (d, J = 3.8 Hz, 1 H), 3.48 (t, J = 8.0 Hz, 1 H), 7.15 (m, 3 H), 7.30--7.45 (m, 6 H), 7.45--7.57(m, 2 H), 7.60--7.70 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.76, 19.19, 23.00, 26.93, 28.72, 33.74, 34.70, 40.77, 45.69, 50.67, 62.75, 126.95, 127.66, 128.94, 129.60, 131.10, 133.72, 133.97, 135.64; exact mass, *m/z* calcd for $C_{31}H_{38}OSeSi$ 534.1857, found 534.1855. Anal. Calcd for $C_{31}H_{38}OSeSi$: C, 69.77; H, 7.18. Found: C, 69.61; H, 7.34.

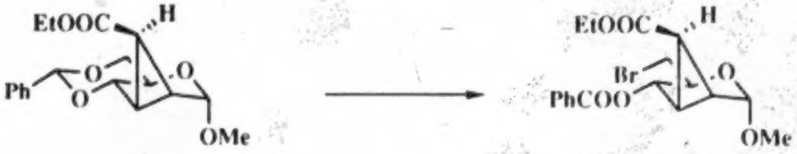
Cis-(1,1-Dimethylethyl)[2-(4-ethyl-2-cyclopenten-1-yl)ethoxy]diphenylsilane (20d).



20c **20d**

The general photochemical method for radical ring opening was followed using selenide **20c** (107 mg, 0.2 mmol) in dry hexane (3 mL) and tributyltin hydride (81 μL, 0.3 mmol). The mixture was stirred and irradiated at 0-10 °C for 45 min, and then at 10-30 °C for 1.5 h. At this stage, some starting material still remained (TLC, silica, 5% ethyl acetate--hexane). Tributyltin hydride (25 μL) was added and the mixture was stirred and irradiated for 40 min at 10-30 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm) using 1% ethyl acetate--hexane afforded **20d** (52 mg 69%) as a slightly yellow oil:# FT-IR ($CHCl_3$ cast) 2957, 2930, 2857, 1582, 1472, 1428, 1112, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, J = 7.5 Hz, 3.6 H), 1.07 (s, 9 H), 1.18--1.60 (m, 3.4 H), 1.75 (dq, J = 13.5, 7.0 Hz, 1 H), 2.18 (dt, J = 12.7, 8.0 Hz, 1 H), 2.52 (m, 1 H), 2.75 (m, 1 H), 3.71 (t, J = 6.9 Hz, 1 H), 5.62 (m, 2 H), 7.32--7.45 (m, 6 H), 7.62--7.73 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 12.31, 19.25, 26.95, 29.54, 37.04, 39.79, 42.41, 47.52, 62.96, 127.64, 129.54, 134.16, 134.69, 135.64; exact mass, *m*/z calcd for $C_{21}H_{25}OSi$ $[(M - C_4H_9)^+]$ 321.1675, found 321.1678. Anal. Calcd for $C_{25}H_{34}OSi$: C, 79.30; H, 9.05. Found: C, 79.39; H, 9.03.

Ethyl [1*R*-(1α,2α,4β,5α,6α,7α)]-5-(Benzoyloxy)-4-(bromomethyl)-2-methoxy-3-oxabicyclo[4.1.0]-heptane-7-carboxylate (21c).



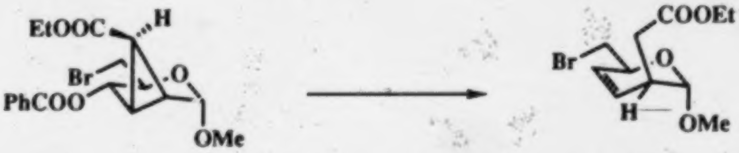
21b **21c**

# The ^{1}H NMR spectrum (200 MHz) showed a byproduct (ca 6mol% of the total). The corrected yield is 65%.

The procedure is based on a general literature method.[52] Barium carbonate (533 mg, 2.7 mmol) and then *N*-bromosuccinimide (freshly recrystallised from water; 354 mg, 1.99 mmol) were each added in one portion to a hot (50 °C) solution of sugar **21b**# (596 mg, 1.8 mmol) in dry carbon tetrachloride (32 mL) contained in a 100-mL round-bottomed flask equipped with a condenser. The oil bath temperature was then raised to 90 °C and the mixture was allowed to reflux for 2 h. The hot solution was filtered through a sintered glass funnel and the insoluble material was washed with hot carbon tetrachloride (4 x 5 mL). The combined filtrates were evaporated and the residue was diluted with ethyl acetate (100 mL). The solution was washed with water (2 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm) using 15% ethyl acetate--hexane afforded **21c** (611 mg, 82%) as a white solid: FT-IR ($CHCl_3$ cast) 1723, 1285, 712 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.0 Hz, 3 H), 1.8 (m, 2 H), 1.93 (dd, J = 5.0, 9.9 Hz, 1 H), 3.37 (dd, J = 11.3, 7.5 Hz, 1 H), 3.55 (s) and 3.56 (dd, J = 11.5, 2.5 Hz) [both signals together correspond to 4 H], 4.0--4.2 [m, including quartets at 4.13 (J = 7.0 Hz) and at 4.14 (J = 7.0 Hz), 3 H], 4.96 (s, 1 H), 5.07 (d, J = 9.2 Hz, 1 H), 7.47 (m, 2 H), 7.62 (m, 1 H), 8.07 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.18. 21.97, 23.09, 24.45, 32.68, 55.68, 61.07, 66.79, 67.13, 96.84, 128.56, 129.32, 129.85, 133.60, 165.55, 171.89; exact mass, *m/z* calcd for $C_{18}H_{21}O_6Br$ 414.0501, found 414.0526. Anal. Calcd for $C_{18}H_{21}BrO_6$: C, 52.31; H, 5.12; O, 23.23; Br,19.34. Found: C, 52.04; H, 5.26; O, 23.18; Br, 20.08.

# Synthesized in four steps from α-Methyl glucoside (reference 37 and 83).

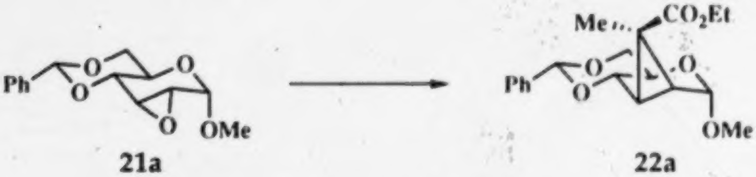
Ethyl [2*S*-(2α,3β,6β)]-6-(Bromomethyl)-3,6-dihydro-2-methoxy-2*H*-pyran-3-acetate (21d).



21c **21d**

The procedure is based on a general literature method.[56] Magnesium perchlorate hexahydrate (152 mg, 0.46 mmol) in water (1 mL), and water (7 mL) were added to a solution of *N*-methylcarbazole (87 mg, 0.482 mmol) and **21c** (181 mg, 0.438 mmol) in distilled THF (80 mL). The mixture was then distributed among four 50-mL test tubes [using distilled THF (3 mL) as a rinse for each tube]. The tubes were capped with septa, flushed with argon and maintained under a static pressure of argon. The tubes were irradiated simultaneously for 10 h at room temperature using a Hanovia 200 W high pressure mercury lamp surrounded by a Pyrex filter. The reaction mixtures were then transferred to a 500-mL round-bottomed flask containing a mixture of saturated aqueous sodium bicarbonate (20 mL) and THF (50 mL). The resulting mixture was evaporated. The residue was extracted with ethyl acetate (2 x 75 mL), and the extracts were washed with saturated aqueous sodium bicarbonate (1 x 40 mL), and 50% brine-water (1 x 40 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm) using 10% ethyl acetate--hexane afforded **21d** (110 mg, 86%) as a colorless oil: FT-IR ($CHCl_3$ cast) 1733, 1370, 1265, 1170, 1120, 1040, 935, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.37--2.64 (m, 3 H), 3.44 (dd, J = 10.8, 5.5 Hz), 3.50 (s), 3.51 (dd, J = 10.8, 4.5 Hz) [the signals at 3.44, 3.50 and 3.51 together correspond to 5 H], 4.16 (q, J = 7.2 Hz, 2 H), 4.43 (m, 1 H), 5.71 (broad d, J = 10.0 Hz, 1 H), 5.89 (dm, J = 10.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.19, 34.95, 35.42, 37.40, 55.67, 60.56, 61.02, 67.37, 100.55, 126.30, 127.39, 171.65; exact mass, *m/z* calcd for $C_{10}H_{14}BrO_3$ [(M - $CH_3O)^+$] 263.0106, found 263.0085. Anal. Calcd for $C_{11}H_{17}BrO_4$: C, 45.06; H, 5.85; O, 21.83. Found; C, 45.27; H, 6.02; O, 21.87.

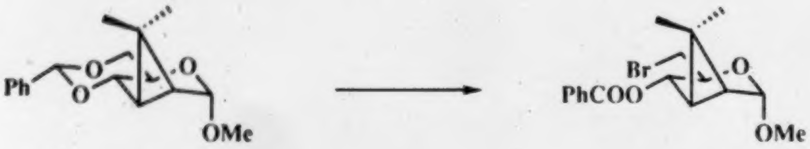
Methyl [2(*R*),4(*R*)]-2,3-Dideoxy-2,3-[1-(ethoxycarbonyl)ethylidene]-4,6-*O*-(phenylmethylene)-α-D-mannopyranoside (22a).



21a **22a**

The literature procedure[38] was followed, but with some modifications. Sodium hydride (7.56 g, 60% suspension in oil, 0.189 mol) was added in several portions over a period of 15 min to a stirred solution of triethyl 2-phosphonopropionate (45.0 g, 0.189 mol) in dry triglyme (150 mL) contained in a 500 mL round-bottomed flask equipped with a condenser. Stirring was continued for 30 min at room temperature, and methyl 2,3-anhydro-4,6-*O*-(phenylmethylene)-α-D-*allo*pyranoside **21a**[83] (10.1 g, 0.0378 mol) was added in one portion. The flask was lowered into an oil bath preheated to 140 °C. Heating at 140 °C was continued for 4 days. The brown solution was allowed to cool to room temperature, and was poured into saturated aqueous ammonium chloride (100 mL). The mixture was extracted with ether (2 x 200 mL), and the combined organic extracts were washed with water (3 x 50 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue (which was applied to the column dissolved in a minimum amount of dichloromethane) over silica gel (6 x 20 cm) using 20% ethyl acetate--hexane afforded **22a** (5.99 g, 45%) as a thick oil containing traces of impurities (TLC, silica, 20% ethyl acetate--hexane): FT-IR ($CHCl_3$ cast) 2977, 2937, 1721 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (t, J = 7.6 Hz, 3 H), 1.38 (s, 3 H), 1.79 (d, J = 11.6 Hz, 1 H), 2.12 (dd, J = 11.6, 2.5 Hz, 1 H), 3.42 (s, 3 H), 3.43--3.51 (m, 1 H), 3.64--3.78 (m, 2 H), 4.11 (q, J = 7.6 Hz, 2 H), 4.23--4.38 (m, 1 H), 4.65 (s, 1 H), 5.60 (s, 1 H), 7.35--7.44 (m, 3 H), 7.47--7.58 (m, 2 H); exact mass, *m*/*z* calcd for $C_{19}H_{24}O_6$ 348.1573, found 348.1556.

[1(*R*)-(1α,2α,4β,5α,6α)]-5-(Benzoyloxy)-4-(bromomethyl)-2-methoxy-7,7-dimethyl-3-oxa-bicyclo[4.1.0]heptane (22c).

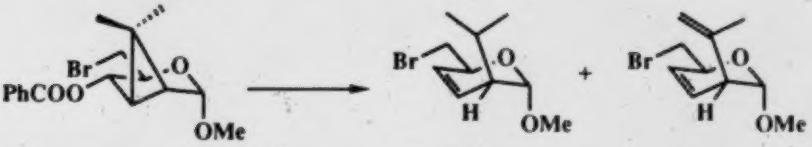


22b **22c**

Barium carbonate (571 mg, 2.89 mmol) and then *N*-bromosuccinimide (freshly recrystallised from water, 377 mg, 2.12 mmol) were added to a hot (65 °C) and stirred solution of methyl 4,6-*O*-(phenylmethylene)-2,3-dideoxy-2,3-C-isopropylidene-α-D-mannopyranoside[38] (555 mg, 1.93 mmol) in carbon tetrachloride (34 mL). Stirring at 65 °C was continued for 1 h and the hot suspension was filtered through a Whatman filter paper (No. 1). The insoluble material was washed with hot carbon tetrachloride (10 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (4.0 x 20 cm) with 10% ethyl acetate--hexane afforded **22b** (501 mg, 71%) as a thick, colorless oil: FT-IR ($CHCl_3$ cast) 2950, 1722, 1274, 1111, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (d, J = 9.1 Hz, 1 H), 1.04 (dd, J = 9.1, 1.9

Hz, 1 H), 1.10 (s, 3 H), 1.25 (s, 3 H), 3.52 (s, J = 11.1, 8.0 Hz, 1 H), 3.58 (dd, J = 11.1, 2.3 Hz, 1 H), 3.89--3.98 (m, 1 H), 4.79 (s, 1 H), 4.85 (dd, J = 8.0, 1.9 Hz, 1 H), 7.43--7.51 (m, 1 H), 7.57--7.63 (m, 1 H), 8.02--8.11 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.42, 17.33, 23.31, 26.09, 27.77, 32.77, 55.18, 67.02, 67.26, 97.52, 128.54, 129.72, 129.80, 133.39, 165.58; exact mass, *m/z* calcd for $C_{17}H_{21}BrO_4$ 370.0603, found 370.0599. Anal. Calcd for $C_{17}H_{21}BrO_4$: C, 55.42; H, 5.75; O, 17.37. Found: C, 55.23; H, 5.72; O, 17.47.

[2*S*(2α,3β,6β)]-6-(Bromomethyl)-3,6-dihydro-3-(1-methylethyl)-2-methoxy-2*H*-pyran (22d) and [2*S*(2α,3β,6β)]-6-(bromomethyl)-3,6-dihydro-3-(1-methylethenyl)-2-methoxy-2*H*-pyran (22e).

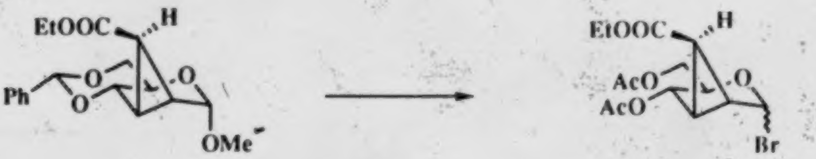


22c **22d** **22e**

Magnesium perchlorate hexahydrate (308 mg, 0.932 mmol) in water (2 mL) and water (7 mL) were added to a solution of *N*-methylcarbazole (169 mg, 0.932 mmol) and **22c** in distilled THF (104 mL). The mixture was then distributed among among four 50-mL test tubes [using distilled THF (3 mL) as a rinse for each tube]. The tubes were capped with septa, flushed with argon and maintained under a static pressure of argon. The tubes were irradiated simultaneously for 7 h at 25 °C using a Hanovia 400 W high pressure mercury lamp surrounded by a Pyrex filter. The mixtures were then transferred to a 500-mL round-bottomed flask containing saturated aqueous sodium bicarbonate (50 mL) and the resulting mixture was evaporated. The residue was extracted with ether (2 x 75 mL) and the extracts were washed with water

(1 x 40 mL), dried ($MgSO_4$), and evaporated. [In this particular run the crude material was kept at -5 °C for 48 h]. Flash chromatography of the residue over silica gel (3 x 20 cm) using mixtures of 2%, 5%, and 40% ethyl acetate--hexane, afforded a 1:1 mixture [^{1}H NMR (300 MHz)] of **22d** and **22e** (140 mg, 67%) as a colorless oil, as well as unidentified material (29 mg). The mixture of **22d** and **22e** had: FT-IR ($CHCl_3$ cast) 2959, 1192, 1117, 1048, 973, 961 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.3 Hz, 3 H), 1.71--1.87 (m, 2.5 H), 1.87--2.03 (m, 1 H), 3.39--3.53 (m, including two singlets at 3.46 and 3.48, 5 H), 4.32--4.44 (m, 1 H), 4.715 (s, 0.5 H), 4.735 (s, 0.5 H), 5.70--5.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.67, 20.53, 21.49, 30.74, 34.71, 34.97, 45.10, 46.95, 55.19, 55.40, 66.87, 67.12, 100.45, 100.48, 113.96, 125.95, 126.02, 126.88, 127.08, 143.74; mass for $C_{10}H_{17}{}^{81}BrO$ and $C_{10}H_{15}{}^{81}BrO$ (chemical ionization, NH_3) 268 (M + 18)$^+$.

(*R*)-4,6,Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-α-D-mannopyranosyl bromide and (*R*)-4,6,Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-β-D-mannopyranosyl bromide (23c).



21b

23c

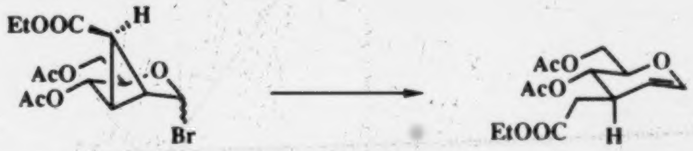
(a) Methyl (*R*)-2,3-Dideoxy-2,3-[(ethoxycarbonyl)-methylene]-α-D-mannopyranoside. A stirred suspension of 5% palladium on carbon (0.5 g) in glacial acetic acid (8 mL) was saturated with hydrogen and **21b**^{37} (1.01 g, 3.04 mmol) was added in one portion. Stirring under 1 atmosphere of hydrogen was continued for 17 h. The catalyst was then removed by filtration through a pad of Celite and the pad was washed with ethyl acetate (5 x 5 mL). The combined filtrates were evaporated and traces of acetic acid were removed by azeotropic evaporation with toluene (15 mL). This evaporation was repeated twice more to afford a white solid which was used without further purification.

(b) Methyl (*R*)-4,6-Di-*O*-acetyl-2,3-Dideoxy-2,3-[(ethoxycarbonyl)-methylene]-α-D-mannopyranoside. Acetic anhydride (0.75 mL, 9.12 mmol) and then 4-(dimethylamino)pyridine (37 mg, 0.3 mmol) were added, each in one portion, to a cold (0 °C) and stirred solution of the above diol (736 mg, 3.04 mmol) in dry pyridine. Stirring was continued for 4 h at room temperature. The mixture was diluted with dichloromethane (70 mL) and washed with aqueous hydrochloric acid 1 M (2 x 25 mL), saturated aqueous sodium bicarbonate (1 x 20 mL), water (1 x 20 mL), and brine (1 x 20 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm) using 30% ethyl acetate--hexane followed by azeotropic evaporation of the new residue with toluene (2 x 15 mL), for removal of traces of pyridine, afforded the required diacetate (881 mg, 88% from the diol) as a white solid: FT-IR ($CHCl_3$ cast) 3050, 1741, 1728, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.2 Hz, 3 H), 1.69 (t, J = 5.0 Hz, 1 H), 1.72--1.82 [m, including a triplet at 1.78 (J = 5.0 Hz), 2 H], 2.09 (s, 3 H), 2.11 (s, 3 H), 3.41 (s, 3 H), 3.86 (ddd, J = 9.4, 5.8, 3.1 Hz, 1 H), 4.03--4.20 (m, 4 H), 4.83 (d, J = 9.6 Hz, 1 H), 4.89 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.15, 20.74, 20.95, 21.94, 22.94, 24.39, 55.09, 60.99, 63.29, 64.10, 64.84, 96.47, 169.92, 170.62, 171.92; exact mass, *m*/*z* for $C_{14}H_{19}O_7$ [$(M - CH_30)^+$] 299.1131, found 299.1133. Anal. Calcd for $C_{15}H_{22}0_8$: C, 54.54; H, 6.71. Found: C, 54.66; H, 6.60.

(c) Methyl (*R*)-1,4,6-Tri-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)-methylene]-α-D-mannopyranose and Methyl (*R*)-1,4,6-Tri-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-β-D-mannopyranose. A solution of sulfuric acid (15 µL) in acetic anhydride (1 mL) was injected over 5 min into a cold (0 °C) and stirred solution of the above mannopyranoside (438 mg, 1.34 mmol) in acetic anhydride (4 mL). Stirring was continued for 4 h at 0 °C. The mixture was diluted with dichloromethane (20 mL) and stirred for 10 min with saturated aqueous sodium bicarbonate (10 mL). The aqueous layer was extracted with dichloromethane (1 x 20 mL) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (1 x 10 mL), and water (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 20 cm) using 40% ethyl acetate--hexane afforded a mixture of the required triacetates in a ratio of 8:1 [^{1}H NMR (200 MHz)] (469 mg, 99%) as a colorless oil: FT-IR ($CHCl_3$ cast) 1746, 1226 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 and 1.33 (two superimposed triplets, J = 7.2 Hz, 3 H), 1.72--1.91 (m, 3 H), 2.10 (s), 2.17 (s), 2.185 (s) and 2.11 (s), 2.16 (s), 2.18 (s) [signals at 2.10, 2.11, 2.16, 2.17, 2.18 and 2.185 together correspond to 6 H], 3.7 (m, 0.11 H), 3.94 (ddd, J = 9.7, 5.1, 3.1 Hz, 1 H), 4.03--4.23 [m, including a quartet at 4.15 (J = 7.2 Hz), 4 H], 4.89 (d, J = 9.2 Hz, 1 H) 6.19 (d, J = 2.2 Hz, 0.11 H), 6.28 (s, 0.89 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (signals due to major isomer only) δ 14.10, 20.64, 20.88, 20.99, 21.72, 21.95, 24.19, 61.19, 62.85, 63.69, 89.36, 169.20, 169.74, 170.59, 171.46; exact mass, *m*/*z* calcd for $C_{16}H_{22}O_9$ 358.1241, found 358.1277. Anal. Calcd for $C_{16}H_{22}O_9$: C,53.62; H, 6.12. Found: C, 53.88; H, 6.27.

(d) (*R*)-4,6,Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-α-D-mannopyranosyl bromide and (*R*)-4,6,Di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-β-D-mannopyranosyl bromide (23c). Trimethylsilyl bromide (37 µL, 0.28 mmol) was injected into a stirred solution of the above triacetates (51 mg, 0.14 mmol) in dry benzene (1.4 mL) contained in a 10-mL round-bottomed flask equipped with a condenser.[51] The mixture was lowered into a bath preheated at 65 °C and stirring was continued for an arbitrary period of 8 h. The mixture was cooled and evaporated (oil pump vacuum) to give the crude bromides **23c** which were used without purification for the next step. The bromides are rather unstable, and, therefore, were kept under argon and protected from moisture.

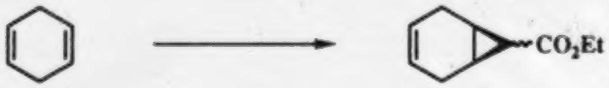
4,6-Di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-3-(2-ethoxy-2-oxoethyl)-D-*arabino*-hex-1-enitol (23d).



23c **23d**

The general procedure for thermal radical ring opening was followed using the crude bromides **23c** (about 0.143 mmol) in dry benzene (1.4 mL), tributyltin hydride (94 µL, 0.35 mmol), and AIBN (2 mg, 0.012 mmol). Refluxing was continued for 2 h, and the mixture was cooled and evaporated. Flash chromatography (twice) of the residue over silica gel (1 x 15 cm) using 25% ethyl acetate--hexane afforded **23d** [34.0 mg, 79% based on the anomeric acetates (see part c above)]: FT-IR ($CHCl_3$ cast) 2980, 1744, 1651, 1374, 1237, 1062, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.09 (s, 6 H), 2.21 (dd, J = 16.0, 9.5 Hz, 1 H), 2.49 (dd, J = 16.0, 5.0 Hz, 1 H), 2.88 (m, 1 H), 3.99 (ddd, J = 10.0, 5.0, 2.4 Hz,1 H), 4.14 (q, J = 7.2 Hz) and 4.17 (d, J = 12.3 Hz) [both signals together correspond to 3 H], 4.36 (dd, J = 12.3, 5.0 Hz, 1 H), 4.68 (dd, J = 6.0, 2.0 Hz, 1 H), 4.97 (t, J = 9.4 Hz, 1 H), 6.38 (dd, J = 6.0, 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.21, 20.76, 20.85, 35.32, 37.29, 60.63, 62.12, 68.83, 74.86, 102.14, 143.06, 170.09, 170.76, 171.68; exact mass, *m/z* calcd for $C_{12}H_{17}O_5$ [(M - $C_2H_3O_2$)$^+$] 255.0869, found 255.0865; mass (chemical ionization, NH_3) 318 [(M + 18)$^+$]. Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 55.78; H, 6.86.

Ethyl (±)-Bicyclo[4.1.0]hept-3-ene-7-carboxylate (37).[58]



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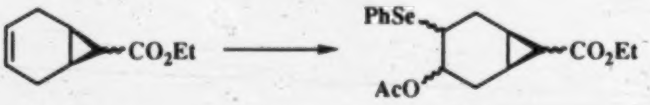
Treatment of 1,4-cyclohexadiene (12.40 g, 0.154 mol) with ethyl diazoacetate (8.8 g, 0.08 mol) in the presence of rhodium(II) acetate (66 mg) at room temperature according to a literature procedure,[58] afforded 37 (8.9 g, 70%) as a mixture of stereoisomers with an endo:exo ratio of 3:7: bp 78-79 °C (*ca*. 5 mm); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19--1.32 [m, including triplets (J = 7.6 Hz) at δ 1.23 and δ 1.28, 3.3 H], 1.40--1.51 (m, 0.6 H), 1.62--1.77 (m, 2.3 H), 2.20--2.56 (m, 4 H), 4.09 (q, J = 7.6 Hz) and 4.13 (q, J = 7.6 Hz) [both signals together correspond to 2 H], 5.48 (broad s, 1.4 H), 5.57 (broad s, 0.6 H).

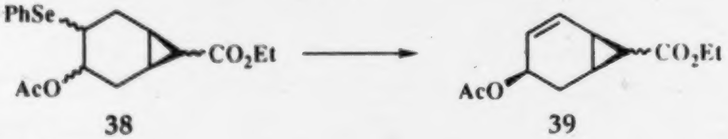
Ethyl (±)-3-Acetoxy-4-(phenylseleno)bicyclo[4.1.0]heptane-7-carboxylate (38).



37 38

Diphenyl diselenide (8.4 g, 26.9 mmol) was added over 1 min to a solution of bromine (4.2 g, 25.2 mmol) in glacial acetic acid (80 mL). The mixture was stirred at room temperature for 10 min, and **37** (7.75 g, 46.7 mmol), followed by anhydrous potassium acetate (9.16 g, 93.4 mmol), were added successively, each in one portion[61]. After being stirred at room temperature for 2 h, the mixture was diluted with ether (500 mL), washed with water (1 x 200 mL), saturated aqueous sodium bicarbonate (1 x 100 mL), and water (1 x 100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (7 x 24 cm) using successively 5%, 8%, and 15% ethyl acetate--hexane afforded **38** (11.56 g, 65%) as a slightly yellow oil that was a mixture of isomers. The major component [*ca* 85 mol%, AcO and C(7) *syn*] had: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.27 (t, J = 7.3 Hz, 3 H), 1.50--2.66 (m, including a singlet at δ 1.97, 1 H), 3.72--3.79 (dm, J = 10.0 Hz, 1 H), 4.11 (q, J = 7.3 Hz, 2 H), 4.79--4.94 (m, 1 H), 7.20--7.33 (m, 3 H), 7.46--7.63 (m, 2 H).

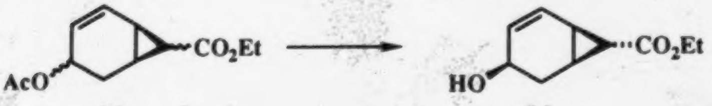
Ethyl (±)-3-Acetoxybicyclo[4.1.0]hept-4-ene-7-carboxylate (39).



Pyridine (4.69 mL, 58 mmol) and then 30% w/w aqueous hydrogen peroxide (6.67 mL, 58 mmol) [addition over 15 min (see the caution in reference 84)] were added to a stirred solution of **38** (from the previous experiment, 11.01 g, 29 mmol) in dichloromethane (130 mL). Stirring was continued for 15 min after the addition of the hydrogen peroxide, and THF (20 mL) was then added in order to obtain an homogeneous mixture. After a further 2 h (stirring), the mixture was diluted with ether (300 mL), washed with 10% w/v aqueous sodium thiosulfate (1 x 100 mL), and water (1 x 100 mL), dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 17 cm) using 15% ethyl acetate--hexane afforded **39** (6.05 g, 93%) as an oil. The material was largely (85 mol%; ^{1}H NMR) a single isomer of the indicated stereochemistry and had: ^{1}H NMR (CDCl$_3$, 300 MHz) (major signals only) δ 1.29 (t, J = 7.2 Hz, 3 H), 1.81 (broad t, J = 4.2 Hz, 1 H), 1.92--2.07 (m, including a singlet at δ 2.04, 1 H), 2.20 (dm, J = 16.0 Hz, 1 H), 4.08--4.21 (m, 2 H), 5.27--5.34 (m, 1 H), 5.73 (dd, J = 10.0, 5.7 Hz, 1 H), 6.32--6.39 (m, 1 H); ^{13}C

NMR ($CDCl_3$, 75.5 MHz) δ 14.22, 20.96, 21.22, 22.16, 24.68, 31.66, 60.54, 65.56, 122.65, 132.60, 170.37, 172.51; exact mass, *m/z* calcd for $C_{12}H_{17}O_4$ 225.1127, found 225.1125.

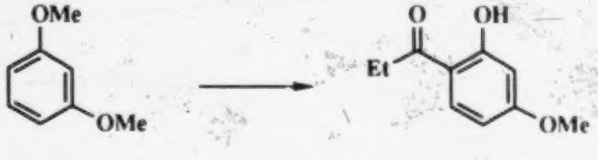
Ethyl (1α,3β,6α,7α)-(±)-3-Hydroxybicyclo[4.1.0]hept-4-ene-7-carboxylate (34).



39 **34**

Sodium hydride (60% dispersion in oil, 203 mg, 5.08 mmol) was added in several portions over 2 min to a stirred solution of **39** (5.72 g, 25.4 mmol) in anhydrous ethanol. After being stirred at room temperature for 2 h, the mixture was quenched with saturated aqueous ammonium chloride (20 mL) and concentrated (water-pump vacuum) to *ca.* 40 mL. The concentrate was diluted with ether (400 mL), washed with water (2 x 50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 21 cm) using 20% ethyl acetate--hexane afforded the allylic alcohol **34** (3.66 g, 79%) as a slightly yellow oil: FT-IR ($CHCl_3$ cast) 3456 (broad), 2981, 2909, 1723, 1702, 1641, 1193 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.0 Hz, 3 H), 1.85--2.01 (m, 4 H), 2.07 (broad d, J = 15.2 Hz, 1 H), 2.51 (broad s, 1 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.26--4.32 (m, 1 H), 5.76 (dd, J = 9.8, 5.2 Hz, 1 H), 6.23 (dd, J = 9.8, 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.14, 21.45, 22.58, 27.29, 32.66, 60.45, 62.52, 127.32, 130.09, 173.06; exact mass, *m/z* calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0942. Anal. Cald for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.29; H, 7.63.

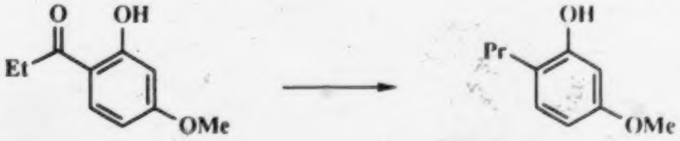
5-Methoxy-2-propionylbenzenol (41).



41

A solution of 1,3-dimethoxybenzene (70.8 g, 0.51 mol) and propionyl chloride (42.23 mL, 0.486 mol) in dry benzene (500 mL) was added dropwise with stirring over 30 min to aluminum trichloride (74 g, 0.56 mol) and the mixture was kept at 25 °C by a water bath.[63] After being stirred at room temperature for 1 h, and then at reflux for 2 h, the mixture was allowed to cool to room temperature and was then carefully treated with cold (0 °C) 1 M aqueous hydrochloric acid (500 mL). The organic layer was separated, dried ($MgSO_4$) and evaporated. Recrystallisation of the residue from 95% ethanol afforded **41** (46.5 g, 47%): FT-IR ($CHCl_3$ cast) 3800--1700, 1631, 1612, 1371, 1206, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, J = 7.4 Hz, 3 H), 2.94 (q, J = 7.4 Hz, 2 H), 3.82 (s, 3 H), 6.38--6.42 (m) and 6.44 (d, J = 2.9 Hz) [both signals together correspond to 2 H], 7.64 (dm, J = 9.5 Hz, 1 H), 12.84 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 8.42, 31.09, 55.45, 100.93, 107.40, 113.29, 131.28, 165.21, 165.81, 205.29 ; exact mass, *m*/*z* calcd for $C_{10}H_{12}O_3$ 180.0787, found 180.0791. Anal. Cald for $C_{10}H_{12}O_3$: C, 66.67; H, 6.67. Found: C, 66.74; H, 6.73

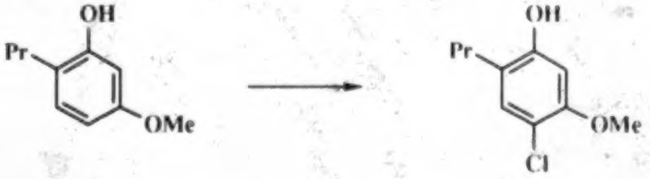
5-Methoxy-2-propylbenzenol (42).



41 **42**

Mercuric chloride (10 g) was added in several portions over 5 min to a suspension of powdered zinc (100 g) in 9 M aqueous hydrochloric acid (75 mL).[64] The phenol **41** (24.9 g) was added in one portion and the mixture was refluxed for 1.5 h, allowed to cool to room temperature, and carefully diluted with 5 M aqueous sodium hydroxide (50 mL). The residue was extracted continuously for 5 h with ethyl acetate, and the solution was dried ($MgSO_4$) and evaporated. The resulting blue oil was distilled to afford pure **42** (20.34 g, 88%) as a colorless oil which slowly solidified to white crystals: (bp 115--118 °C, 0.34 mm); FT-IR ($CHCl_3$ cast) 3405, 2940, 1620, 1593, 1519, 1161, 1123 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.2 Hz, 3 H), 1.60 (sextet, J = 7.2 Hz, 2 H), 2.50 (broad t, J = 7.2 Hz, 2 H), 3.64 (s, 3H), 5.20 (s, 1 H), 6.36 (d, J = 2.4 Hz, 1 H), 6.44 (dd, J = 9.0, 2.4 Hz, 1 H), 7.0 (d, J = 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.92, 23.14, 31.31, 55.34, 101.73, 105.95, 120.84, 130.63, 154.27, 158.76; exact mass, *m*/*z* calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0992. Anal. Cald for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.57; H, 8.60.

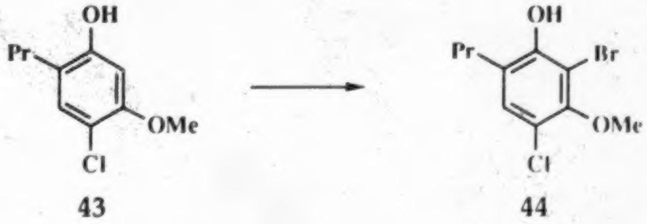
4-Chloro-5-methoxy-2-propylbenzenol (43).



42 **43**

A solution of freshly distilled sulfuryl chloride (5.58 mL, 69.42 mmol) in dry ether (20 mL) was added dropwise over 15 min (syringe pump) to a stirred solution of **42** (11.9 g, 66.1 mmol) in the same solvent (60 mL).[65] After 30 min, more sulfuryl chloride (1.1 mL, 13.68 mmol) in dry ether (5 mL) was added over 3 min and stirring was continued for 1 h. The mixture was then concentrated (water-pump), diluted with ether (200 mL) and water (200 mL), and stirred for 40 min. The organic layer was separated and washed with water (1 x 100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography (twice) of the brown residue over silica gel (7 x 12 cm) using 10% ethyl acetate--hexane afforded **43** (9.88 g, 70%) as a yellow oil which becomes black within hours at room temperature but which remains pure for at least 3 days at room temperature as judged by ^1H NMR and combustion analysis measurements: FT-IR ($CHCl_3$ cast) 3450, 2960, 1511, 1205, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 7.2 Hz, 3 H), 1.59 (sextet, J = 7.2 Hz, 2 H), 2.47 (t, J = 7.2 Hz, 2 H), 3.78 (s, 3 H), 5.23 (broad s, 1 H), 6.41 (s, 1 H), 7.07 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.79, 22.91, 31.01, 56.22, 100.79, 113.36, 121.35, 130.84, 152.85, 153.55; exact mass, *m*/*z* calcd for $C_{10}H_{13}{}^{35}ClO$ and $C_{10}H_{13}{}^{37}ClO$, 200.0604 and 202.0575, found 200.0618 and 202.0591. Anal. Cald for $C_{10}H_{13}ClO$: C, 59.85; H, 6.53. Found: C, 59.66; H, 6.50.

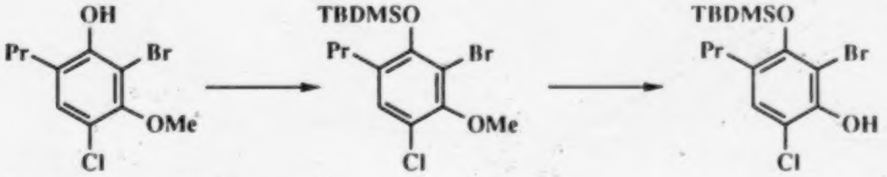
2-Bromo-4-chloro-3-methoxy-6-propylbenzenol (44).



Bromine (7.29 g, 45.53 mmol) in glacial acetic acid (25 mL) was added dropwise over 15 min (syringe pump) to a stirred solution of **43** (7.29 g, 33.8 mmol) in the same solvent (70 mL). After 45 min, the solvent was evaporated and the residue was diluted with ether (250 mL), washed with water (2 x 100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the resulting red oil over silica gel (70 x 180 mm) using 5% ethyl acetate--

hexane afforded **44** (9.2 g, 92%) as a reddish transparent oil that was 90 mol% pure [^{1}H NMR, (300 MHz)]: FT-IR ($CHCl_3$ cast) 3507, 2960, 1477, 1431, 1398, 1157 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) (major signals only) δ 0.94 (t, J = 7.2 Hz, 3 H), 1.60 (sextet, J = 7.2 Hz, 2 H), 2.59 (t, J = 7.2 Hz, 2 H), 3.86 (s, 3 H), 5.58 (s, 1 H), 7.09 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.86, 22.61, 32.31, 60.64, 106.87, 119.03, 126.56, 129.73, 149.94, 151.01; mass for $C_{10}H_{12}{}^{79}Br^{35}ClO_2$, $C_{10}H_{12}{}^{79}Br^{37}ClO_2$ and $C_{10}H_{12}{}^{81}Br^{37}ClO_2$ (chemical ionization, NH_3) 296 (M + 18)$^+$, 298 (M' + 18)$^+$ and 300 (M'' + 18)$^+$. Anal. Cald for $C_{10}H_{12}BrClO_2$: C, 42.96; H, 4.33; O, 11.45. Found: C, 42.44; H, 4.25; O, 11.30.

2-Bromo-6-chloro-3-[dimethyl(1,1-dimethylethyl)silyl]oxy-4-propylbenzenol (45).

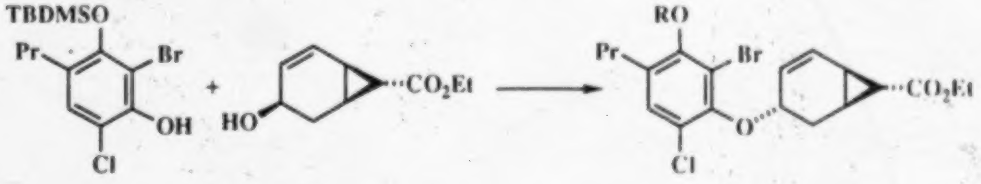


44 **45**

tert-Butylchlorodimethylsilane (2.67 g, 17.7 mmol) was added in one portion to a stirred solution of **44** (90 mol% pure, 5.0 g, 18.0 mmol) and imidazole (2.52 g, 37.1 mmol) in dry dimethylformamide (40 mL). After 1.5 h, the mixture was diluted with ether (350 mL) and washed with water (1 x 200 mL). The aqueous layer was extracted with ether (1 x 150 mL) and the combined organic layers were washed with water (1 x 200 mL), dried ($MgSO_4$) and evaporated. Filtration of the residue through silica gel (7 x 15 cm) using 6% ethyl acetate--hexane afforded impure silyl ether (6.5 g) which was used directly in the next step without further purification.

Boron tribromide (1 M in dichloromethane, 20.7 mL, 20.7 mmol) was added over 2 min to a cold (-78 °C) and stirred solution of crude silyl ether (6.5 g, 16.57 mmol) in dry dichloromethane (100 mL). Stirring at 0 °C was continued for 1.5 h, and the mixture was quenched with saturated aqueous sodium bicarbonate (100 mL) and diluted with ether (300 mL). The organic extracts were washed with water (100 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (7 x 18 cm) using 1% ethyl acetate--hexane afforded pure **45** (5.56, 82% from **44**): FT-IR ($CHCl_3$ cast) 3507, 2958, 2930, 1468, 1424, 1191, 833, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.27 (s, 6 H), 0.91 (t, J = 7.2 Hz, 3 H), 1.03 (s, 9 H), 1.54 (sextet, J = 7.2 Hz, 2 H), 2.50 (t, J = 7.2 Hz, 2 H), 4.25--5.75 (broad, 1 H), 7.07 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -2.44, 13.78, 18.92, 23.29, 26.20, 32.61, 104.69, 112.64, 127.26, 128.58, 147.24, 150.36; mass for $C_{15}H_{24}{}^{79}Br^{35}ClO_2Si$, $C_{15}H_{24}{}^{79}Br^{37}ClO_2Si$ and $C_{15}H_{24}{}^{81}Br^{37}ClO_2Si$ (chemical ionization, NH_3) 396 $(M + 18)^+$, 398 $(M' + 18)^+$, 400 $(M'' + 18)^+$. Anal. Cald for $C_{15}H_{24}BrClO_2Si$: C, 47.43; H, 6.37; Halogens (based on Cl), 18.66. Found: C, 47.19; H, 6.25; Halogens (based on Cl), 18.28.

Ethyl (1α,3α,6α,7α)-(±)-3-(2-Bromo-6-chloro-3-hydroxy-4-propylphenoxy)bicyclo[4.1.0]hept-4-ene-7-carboxylate (46).



45 34 47

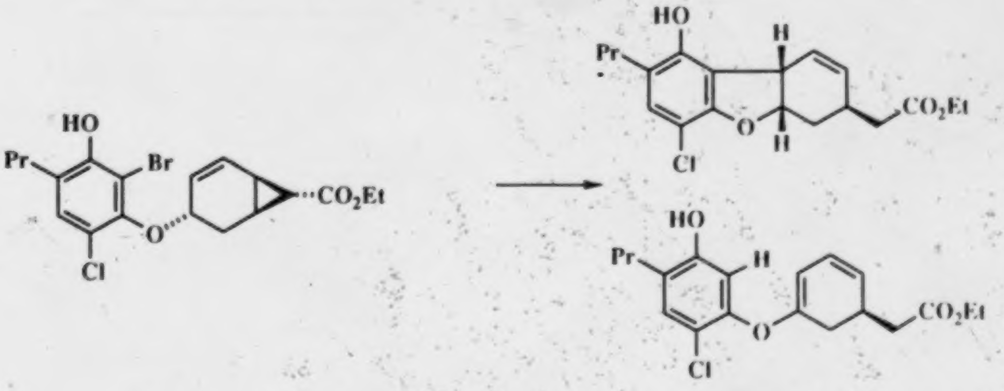
Diethyl azodicarboxylate (1.87 g, 1.69 mL, 10.7 mmol) was added over 2 min to a cold (-40 °C) and stirred solution of triphenylphosphine (2.83 g, 10.8 mmol) in dry THF (60 mL). After 30 min at -40 °C, the mixture became a thick paste and was therefore allowed to attain room temperature (over 30 min), and then diluted with dry THF (30 mL). The suspension, which could now be stirred, was cooled to -30 °C and alcohol **34** (1.98 g, 10.9 mmol) in dry THF (7 mL + 2 mL rinse) was injected over 3 min by cannula. After being stirred at -30 °C for 1 h, and then at -20 °C for 1 h, phenol **45** (1.65 g, 4.35 mmol) in dry THF (5 mL + 2 mL rinse) was added over 2 min by cannula to the suspension. All the solids dissolved as soon as the addition was complete. The solution was stirred at -20 °C for 1 h and the solvents were then evaporated. Flash chromatography of the residue over silica gel (7 x 18 cm) using 4% ether--hexane afforded **46** (1.92 g). The material contained some impurities but was used directly in the next step: FT-IR ($CHCl_3$ cast) 29.58, 1726, 1458, 1180, 855 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.28 (s, 6 H), 0.93 (t, J = 7.8 Hz, 3 H), 1.03 (s, 9 H), 1.24 (t, J = 7.2 Hz, 3 H), 1.49--1.61 (m, 3 H), 1.90--1.99 (m, 2 H), 2.03--2.15 (m, 1 H), 2.49--2.61 (m, 3 H), 4.11 (q, J = 7.1 Hz, 2 H), 4.55--4.64 (m, 1 H), 5.89 (broad d, J = 10.3 Hz, 1 H), 6.10 (dm, J = 10.3 Hz, 1 H), 7.09 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -2.35, 13.82, 14.25, 18.93, 19.30, 20.46, 23.04, 25.07, 26.21, 26.89, 32.80, 60.58, 75.58, 113.15, 120.84, 126.99, 127.61, 129.29, 131.19, 150.01, 150.75, 172.64; exact mass, for $C_{25}H_{36}{}^{79}Br^{35}ClO_4Si$ (chemical ionization, NH_3) 560 (M + 18)$^+$. Anal. Cald for $C_{25}H_{36}BrClO_4Si$: C, 55.19; H, 6.67; Halogens (based on Cl), 13.04. Found: C, 55.25; H, 6.81; Halogens (based on Cl), 12.77.

The reaction is capricious; on a few occasions lower yields (30-70%) were obtained

Tetrabutylammonium fluoride (1 M in THF, 6 mL, 7.06 mmol) was added in one portion to a stirred solution of crude silyl ether of **46** (1.92 g, *ca.* 3.5 mmol) in dry THF (20 mL). After 1.5 h, the mixture was diluted with ether (200 mL), washed with water (2 x 50 mL), dried ($MgSO_4$) and evaporated. Flash chromatography (twice) of the residue over silica gel (4 x 19 cm) using first 8% and then 10% ethyl acetate--hexane afforded pure **47** (1.19 g, 64% from phenol **45**) as a colorless oil: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.96 (t, J = 7.8 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.53--1.87 (m, 3 H), 1.97--2.02 (m, 2 H), 2.03--2.18 (m, 1 H), 2.55--2.70 (m, 3 H), 4.16 (q, J = 7.1 Hz, 2 H), 4.58--4.72 (m, 1 H), 5.65 (s, 1H), 5.89 (broad d, J = 10.3 Hz, 1 H), 6.15 (dm, J = 10.3 Hz, 1 H), 7.11 (s, 1 H).

In a previous run on *ca.* 1/10 scale, the yield from phenol **45** was 75%.

Ethyl (3α,4aα,9bα)-(±)-(6-chloro-9-hydroxy-8-propyl-3,4,4a,9b-tetrahydrodibenzofuran-3-yl)acetate (48) and Ethyl (±)-[3-(6-chloro-3-hydroxy-4-propylphenoxy)cyclohexa-3,5-dienyl]acetate (49).



47

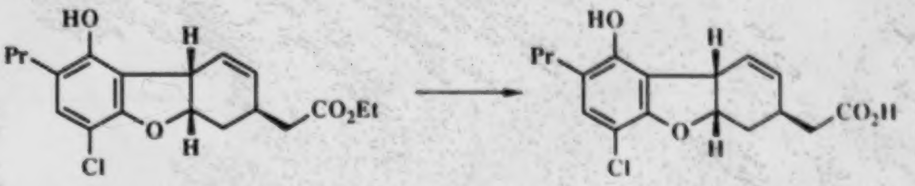
48 and **49**

Triethylborane (1 M in hexane, 0.17 mL, 0.17 mmol) and then tributyltin hydride (47 μL, 0.17 mmol) were added to a solution of **47** (48 mg, 0.111 mmol) in dry benzene (distilled over CaH$_2$, 10 mL) and the mixture was stirred for 24 h. The solvent was evaporated and the residue was diluted with ether (3 mL) and stirred with an excess of potassium fluoride in water. After 1 h, the mixture was diluted with ether (10 mL) and the organic layer was washed with water (3 mL), dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 12 cm) using successively

10%, 15% and 20% ethyl acetate--hexane afforded **48** (17 mg, 43%) as a white solid and **49** (7 mg, 18%) as colorless oil. Compound **48** had: mp 124-130 °C; FT-IR ($CHCl_3$ cast) 3402, 2951, 1714, 1614, 1479, 1280, 1250, 1215, 1195, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1,0 (t, J = 7.5 Hz, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.42--1.75 (m, 3 H), 2.35--2.55 (m, 5 H), 2.80--3.0 (m, 1 H), 3.93--4.02 (m, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 4.71 (broad s, 1 H), 5.08--5.18 (m, 1 H), 5.76 (d, J = 10.2 Hz, 1 H), 5.88 (dt, J = 10.2, 3.2 Hz, 1 H), 6.86 (s, 1 H); [Irradiation at δ 5.8 caused the signal at δ 3.93--4.02 to collapse to a dd (J = 8.0 Hz, 1.2 Hz), the signal at δ 2.80--3.0 to simplify slightly. Irradiation at δ 3.98 caused the signal at δ 5.88 to collapse to a dd (J = 10.0, 3.2 Hz), the signal at δ 5.08--5.18 to collapse to a triplet (J = 3.6 Hz). Irradiation at δ 2.88 caused the signal at δ 1.42--1.75 to simplify, the signal at δ 2.35--2.55 to simplify, the signal at δ 3.93--4.2 to collapse to a dd (J = 7.6, 2.0 Hz), and the signal at δ 5.88 to collapse to a dd (J = 10.0, 3.2 Hz)]; ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.82, 14.20, 23.13, 26.61, 31.13, 31.29, 39.87, 40.16, 60.65, 82.17, 106.31, 118.13, 122.14, 125.11, 129.15, 131.15, 149.10, 154.20, 172.54; exact mass, *m/z* calcd for $C_{19}H_{23}ClO_4$ (^{35}Cl) 350.1285 and (^{37}Cl) 352.1255, found (^{35}Cl) 350.1286 and (^{37}Cl) 352.1263. Anal. Cald for $C_{19}H_{23}ClO_4$: C, 65.04; H, 6.61; O, 18.24. Found: C, 64.88; H, 6.50; O, 17.97. Compound **49** had: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.01 (t, J = 7.2 Hz, 3 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.60--1.80 (m, 2 H), 2.34 (dd, J = 16.0, 8.0 Hz, 1 H), 2.45--2.59 (m) and 2.67 (ddd, J = 16.0, 7.6, 0.8 Hz) [both signals together correspond to 3 H], 2.92--3.12 (m, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 4.95 (d, J = 1 H), 5.14 (s, 1 H), 5.48 (dd, J = 8.8, 4.8 Hz, 1 H), 5.83 (ddd, J = 8.8, 6.0, 1.6 Hz, 1 H), 6.58 (s, 1 H), 7.13 (s, 1 H).

The radical reaction is initiated by traces of oxygen in the solvent.[50] In a subsequent run, where benzene freshly distilled over sodium--benzophenone ketyl, was used the reaction was sluggish and required a large excess of triethylborane and tin hydride.

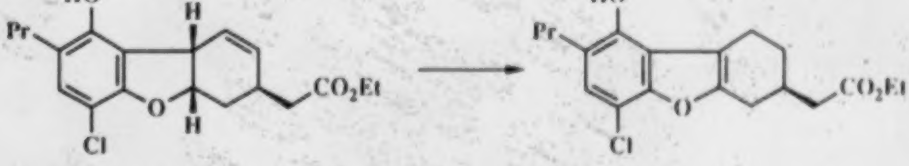
(3α,4aα,9bα)-(±)-(6-Chloro-9-hydroxy-8-propyl-3,4,4a,9b-tetrahydrodibenzofuran-3-yl)acetic acid (50)



48 **50**

Lithium hydroxide monohydrate (33 mg, 0.78 mmol) was added to a stirred solution of **48** (55 mg, 0.157 mmol) in 60% THF-water. After 8 h, the mixture was diluted with ether (6 mL) and water (6 mL). The aqueous layer was separated, acidified to pH 2 using 6 M aqueous hydrochloric acid and extracted with ether (2 x 6 mL). The organic extracts were dried ($MgSO_4$) and evaporated to yield the desired carboxylic acid **50** (50 mg, 100%) as a brownish solid: mp 176-181 °C; FT-IR (THF cast) 3700--2100, 2959, 1708, 1617, 1473, 1428, 1275, 1235, 1208 cm^{-1}; ^1H NMR (THF-d_8, 200 MHz) δ 0.95 (t, J = 7.1 Hz, 3 H), 1.48--1.68 (m, 3 H), 2.30 (d, J = 7.2 Hz, 2 H), 2.36--2.58 (m, 3 H), 2.68--2.88 (m, 1 H), 3.89--3.99 (m, 1 H), 4.97--5.07 (m, 1 H), 5.70 (d, J = 10.5 Hz, 1 H), 5.81 (dt, J = 10.5, 2.5 Hz, 1 H), 6.78 (s, 1 H), 7.15--8.6 (broad, 1 H); exact mass, *m/z* calcd for $C_{17}H_{19}ClO_4$ 322.0971, found 322.0962.

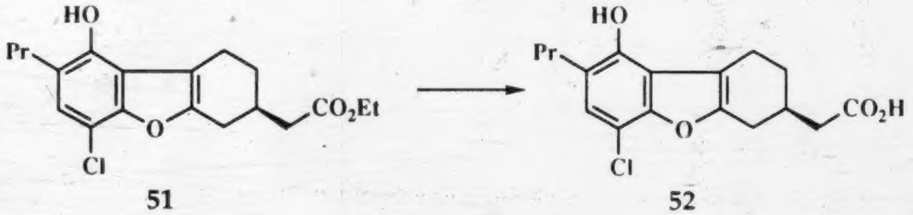
Ethyl (±)-(6-chloro-9-hydroxy-8-propyl-1,2,3,4-tetrahydrodibenzofuran-3-yl)acetate (51).



48 **51**

Rhodium chloride trihydrate (50 mg, 0.21 mmol) was added to a stirred solution of **48** (150 mg, 0.428 mmol) in 20% ethanol--benzene (6 mL) contained in a 10-mL round-bottomed flask equipped with a condenser[66]. The flask was lowered into an oil bath preheated at 65 °C and the mixture was stirred at that temperature for 18 h, allowed to cool to room temperature and evaporated. Flash chromatography of the black residue over silica gel (1.5 x 12 cm) using 20% ethyl acetate--hexane afforded **51** (125 mg, 84%) as a white solid: mp 123-124 °C;FT-IR ($CHCl_3$ cast) 3499, 1717, 1474, 1195, 854 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.01 (t, J = 7.4 Hz, 3 H), 1.32 (t, J = 7.0 Hz, 3 H), 1.68 [sextet (J = 7.5 Hz) superimposed on a multiplet, 3 H], 2.00--2.11 (m, 1 H), 2.40--2.60 (m) and 2.60 (t, J = 7.8 Hz) [both signals together correspond to 6 H], 2.80--3.10 (m, 3 H), 4.20 (q, J = 7.0 Hz, 2H), 4.79 (s, 1 H), 6.95 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.79, 14.20, 20.74, 23.37, 28.59, 29.14, 30.97, 31.14, 40.08, 60.51, 107.73, 112.02, 118.68, 121.94, 124.57, 145.74, 149.67, 152.20, 172.55; exact mass, *m/z* calcd for $C_{19}H_{23}ClO_4$ (^{35}Cl) 350.1285 and (^{37}Cl) 352.1255, found (^{35}Cl) 350.1289 and (^{37}Cl) 352.1267. Anal. Cald for $C_{19}H_{23}ClO_4$: C, 65.04; H, 6.61; O, 18.24. Found: C, 65.15; H, 6.54; O, 18.07.

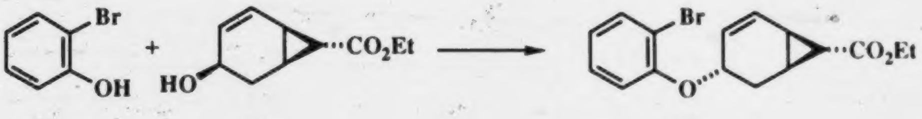
(±)-(6-Chloro-9-hydroxy-8-propyl-1,2,3,4-tetrahydrodibenzofuran-3-yl)acetic acid (52).



Hydrolysis of **51** (55 mg), under identical conditions to those used for **48**, afforded acid **52** (50 mg, 100%) as a solid: mp 205-207 °C; FT-IR (THF cast)

3700--2100 (including peak at 3486), 1685, 1474, 1344, 1280, 1184, 852 cm^{-1}; ^{1}H NMR (THF-d_8, 300 MHz) δ 1.0 (t, J = 7.6 Hz, 3 H), 1.50--1.78 (m, 3 H), 1.95--2.15 (m, 1 H), 2.30--2.60 (m, 4 H), 2.66 (t, J = 7.9 Hz, 2 H), 2.74--3.11 (m, 3 H), 6.92 (s, 1 H), 7.55 (br, 1 H); exact mass, *m/z* calcd for $C_{17}H_{19}{}^{35}ClO_4$ 322.0972, found 322.0968.

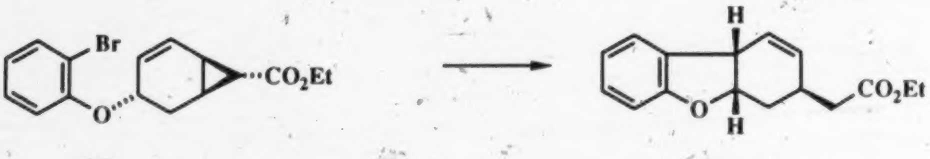
Ethyl (1α,3α,6α,7α)-(±)-3-(2-Bromophenoxy)bicyclo[4.1.0]hept-4-ene-7-carboxylate (35).



33 34 35

Diethyl azodicarboxylate (0.21 mL, 1.32 mmol) was added over 2 min to a cold (-40 °C) and stirred solution of triphenylphosphine (0.35 g, 1.32 mmol) in dry THF (8 mL). After 30 min at -40 °C, the mixture became a thick paste and was therefore allowed to attain room temperature (over 30 min) and diluted with dry THF (5 mL). The suspension, which could now be stirred, was cooled to -40 °C and alcohol **34** (240 mg, 1.32 mmol) in dry THF (2 mL + 1 mL rinse) was injected over 3 min by cannula. After being stirred at -40 °C for 1 h, and then at -20 °C for 1 h, *o*-bromophenol (81 μL, 0.66 mmol) was injected over 2 min. All the solids dissolved as soon as the addition was complete. With the cold bath left in place, the mixture was allowed to attain room temperature (over *ca.* 1 h) and the solvents were then evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm) using 12% ether--hexane afforded crude **35** which was further purified using a Chromatotron [circular plate coated with a 2 mm-thick adsorbent (silica gel 60 PF_{254} containing gypsum)]. Successive elution with 4%, 8%, and 12% ether--hexane gave pure **35** (72 mg, 33%) as a colorless oil: FT-IR ($CHCl_3$ cast) 1720, 1475, 1183 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.0 Hz, 3 H), 1.63 (t, J = 3.8 Hz, 1 H), 1.82--2.03 (m, 3 H), 2.55--2.70 (m, 1 H), 4.13 (q, J = 7.0 Hz, 2 H), 4.55--4.65 (m, 1 H), 5.72 (broad d, J = 10.2 Hz, 1 H), 6.18 (dm, J = 10.2 Hz, 1 H), 6.82--6.93 (m, 2 H), 7.20--7.30 (m, 1 H), 7.50--7.57 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.26, 19.09, 20.39, 24.60, 27.09, 60.71, 71.32, 113.63, 115.77, 122.58, 126.50, 127.94, 128.36, 133.68, 154.31, 172.52; exact mass, *m/z* calcd for $C_{16}H_{17}{}^{79}BrO_3$ 336.0362, found 336.0350. Anal. Cald for $C_{16}H_{17}BrO_3$: C, 56.98; H, 5.08; O, 14.23. Found: C, 56.84; H, 4.91; O, 14.28.

Ethyl (3α,4aα,9bα)-(±)-(3,4,4a,9b-Tetrahydrodibenzofuran-3-yl)acetate (36).

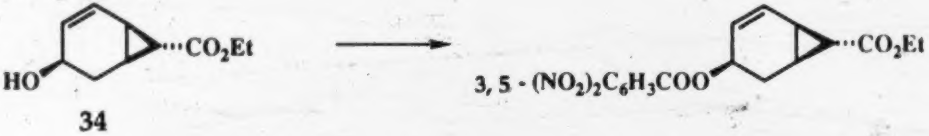


35 36

Triethylborane (1 M in hexane, 0.22 mL, 0.22 mmol) and then tributyltin hydride (0.231 mL, 0.878 mmol) were added to a stirred solution of **35** (140 mg, 0.439 mmol) in dry hexanes (18 mL). The mixture was stirred at 35 °C for 24 h. The solvent was then evaporated and the residue was diluted with ether (6 mL) and stirred with an excess of potassium fluoride in water. After 1 h, the mixture was diluted with ether (20 mL) and the organic layer was washed with water (6 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 12 cm) using 5--10% ethyl acetate--hexane afforded **36** (71 mg, 67 %) and an unidentified side product (12 mg). Compound **36** had: FT-IR ($CHCl_3$ cast) 2860, 1731, 1597, 1477, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.2 Hz, 3 H), 1.58--1.78 (m, 2 H), 2.31--

2.41 (m, including a doublet at δ 2.35, (J = 7.2 Hz), 3 H), 2.72--2.92 (m, 1 H), 3.79 (broad d, 7.2 Hz, 1 H), 4.17 (q, J = 7.2 Hz, 2 H), 5.06 (m, 1 H), 5.72 (broad s, 2 H), 6.77--6.90 (m, 2 H), 7.05--7.12 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.30, 26.90, 31.49, 40.25, 41.06, 60.45, 80.70, 109.94, 120.58, 124.51, 127.19, 128.28, 130.78, 130.86, 159.37, 172.12; exact mass, *m/z* calcd for $C_{16}H_{18}O_3$ 258.1255, found 258.1252.

Ethyl (1α,3β,6α,7α)-(±)-3-[3,5-Dinitrobenzoyloxy]bicyclo[4.1.0]hept-4-ene-7-carboxylate.



Freshly recrystallized 3,5-dinitrobenzoyl chloride (140 mg, 0.61 mmol), and then a few crystals of 4-(dimethylamino)pyridine were added in one portion to a stirred solution of **34** (85 mg, 0.47 mmol) in dry pyridine (1 mL). Stirring at room temperature was continued for an arbitrary period of 6 h and the mixture was then evaporated under reduced pressure. The residue was diluted with dichloromethane (20 mL) and the solution was washed with cold 1N aqueous hydrochloric acid (2 x 5 mL), saturated aqueous sodium bicarbonate (1 x 5 mL), and water (1 x 5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 18 cm) using 15% ethyl acetate--hexane afforded the dinitrobenzoate derivative of **34** (ca 150 mg) as a white solid. Recrystallization from dichloromethane--hexane gave colorless thin crystals: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (t, J = 7.8 Hz, 3 H), 1.95 (t, J = 3.8 Hz, 1 H), 2.10--2.26 (m, 3 H), 2.38--2.54 (m, 1 H), 4.16 (q, J = 7.8 Hz, 2 H), 5.61--5.72 (m, 1 H), 5.86 (dd, J = 10.0, 6.0 Hz, 1 H), 6.46--6.60 (dm, J = 10.0 Hz, 1 H), 9.04--9.12 (m, 2 H), 9.16--9.24 (m, 1 H).

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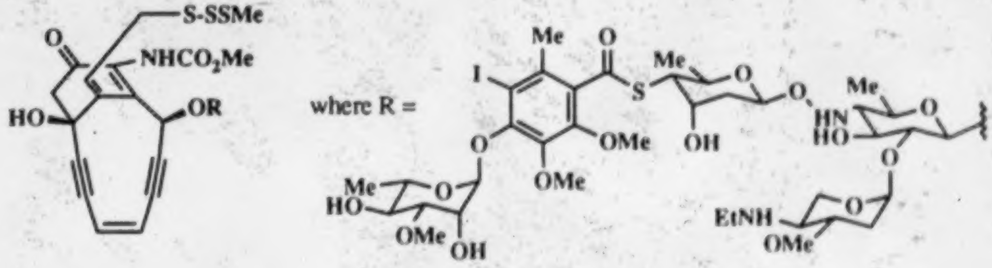
CHAPTER 2

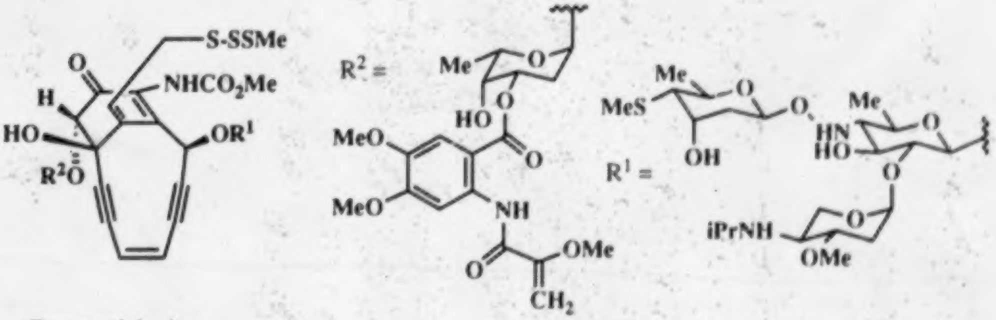
PRELIMINARY STUDIES ON THE SYNTHESIS OF CALICHEAMICINONE

I. INTRODUCTION

Over the past four years considerable efforts have been devoted to elucidation of the structures and mechanism of action of a series of novel naturally occurring compounds called calicheamicins[1] and esperamicins.[2]

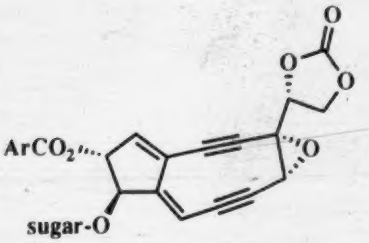

S-SSMe
O
NHCO$_2$Me
HO
OR
where R =
Me
O
I
S
O
Me
O
HN
HO
O
OMe
OH
OMe
Me
HO
O
OMe
OH
EtNH
O
OMe

Calicheamicin γ_1^I

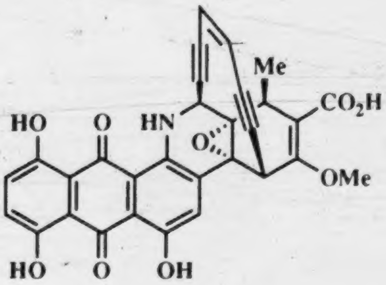

S-SSMe
O
H
NHCO$_2$Me
HO
OR^1
R^{2}O
R^2 =
Me
O
O
HO
MeO
O
MeO
NH
O
OMe
CH$_2$
Me
MeS
O
O
Me
OH
HN
HO
O
R^1 =
O
iPrNH
O
OMe

Esperamicin A_1

The compounds, which have powerful biological properties, were isolated from *Micromonospora echinospora* ssp calichensis and cultures of *Actinomadura verrucospora*, respectively. They are prominent members of a growing class of antitumor agents characterized by the presence of an enediyne moiety. Other members of this class include the previously discovered neocarzinostatin,[3] the very recently discovered dynemicin A,[4] as well as similar (or identical compounds) identified as FR-900405, FR-900406[5] and the veractamycins PD114,759 and PD115,208.[6]



Neocarzinostatin



Dynemicin A

These substances have attracted enormous attention because of their complex and unusual structures, which represent a substantial challenge for synthetic organic chemists, and also because of their strong potency against murine tumors. The compounds are among the most powerful antitumor agents known.

The mode of action is believed to involve Bergman rearrangement of the 1,5-diyne-3-ene into a diyl radical which attacks DNA.

A very large number of synthetic studies have been reported in this area, some of them being aimed at constructing the central core enediyne bicyclic system, while others involve the peripheral carbohydrate attachments. The requirements for triggering the Bergman rearrangement are also being explored. All of these subjects are surveyed in the following paragraphs with emphasis on studies related to the calicheamicins.

The structure of calicheamicin $\gamma_1{}^I$ was recently elucidated, although the stereochemistry at one of the centers was revised shortly afterwards. The structure consists of two major portions. The first is represented by four sugar units, two of them being linked by a unique N-O glycosidic bond, and a fully substituted iodothiobenzoate moiety. The aglycon portion is a bicyclo[7.3.1]tridec-9-ene-2,6-diyne with a methyl trisulfide attachment, and an α,β-unsaturated ketone substructure bearing a methoxycarbonylamino group on the α carbon.

(A) BIOLOGICAL ASPECTS

Calicheamicin $\gamma_1{}^I$ is 4000 times more active than adriamycin against murine tumors and its optimal dose is 0.5 to 1.5 μg per kilogram of body weight.[7] The drug can also cause chromosome aberrations in human lung fibroblasts and mutagenesis in *Escherichia Coli*.

The antimicrobial and antitumor properties of the calicheamicins (and esperamicins) follows from their capacity to cut single and double stranded DNA.[8] Evidence has been accumulated that the effector species for DNA degradation *in vitro* is a benzene diyl arising from chemically induced Bergman bond reorganization of the 1,5-diyne-3-ene moiety (Scheme 1).[8,#,##]

In vivo, this reorganization would be triggered by bioreductive activation of calicheamicin, resulting in conversion of the methyl trisulfide into a thiolate. The latter attacks the α,β-unsaturated ketone in a Michael fashion, resulting in saturation of the bridgehead double-bond, thus

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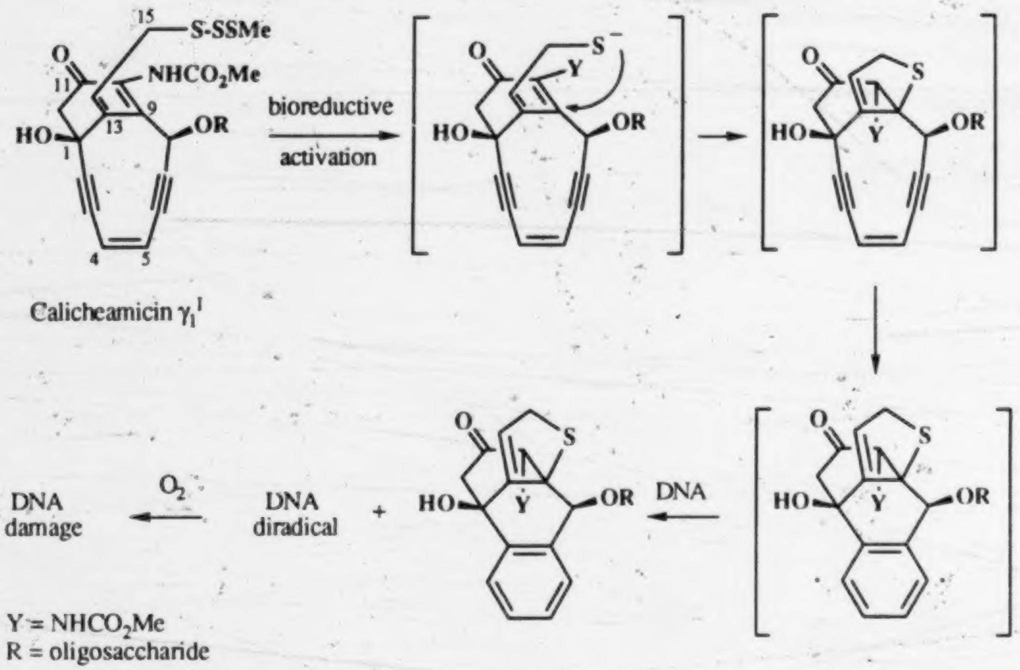
[#] For studies that demonstrate for the first time the existence of an intermediate benzenediyl, see reference 9.

[##] For calculations leading to the conclusion that the cyclization of calicheamicin/esperamicin analogs involves a biradicaloid transition state, see reference 10.

SCHEME 1

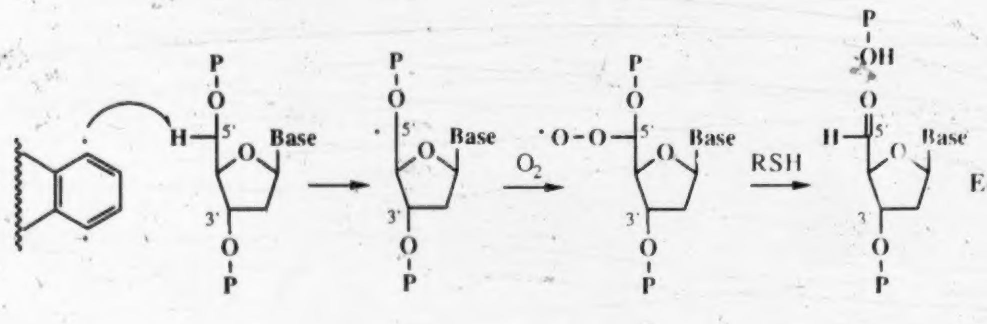

15
S-SSMe
O
11
NHCO2Me
9
13
HO
1
OR
4
5
Calicheamicin γ1I
bioreductive
activation
S−
Y
S
Ẏ
DNA
DNA diradical
+
O2
DNA damage
Y = NHCO2Me
R = oligosaccharide

changing the hybridization at C-1 from sp^2 to sp^3. This change in hybridization allows the two triple bonds to approach each other so that the ends of the enediyne [C-3 and C-7] are close enough for cyclization to take place so as to form a phenylene diradical (Bergman cycloaromatization).[11]

This diradical is believed to be the active form of the drug. It is responsible for abstracting a hydrogen atom from the sugar phosphate backbone of DNA, producing single and double-strand DNA cleavage. In some instances, the drug identifies sites for DNA degradation with remarkable sequence specificity.[12]

In the presence of thiol cofactors,[7] calicheamicin $\gamma_1{}^I$ at concentrations as low as 0.01 μg/mL (7 nM) causes double strand and single strand breaks in supercoiled ϕX174 DNA. In the absence of thiol cofactors, only slight cutting was observed at 0.1 μg/mL. At 0.1 μg/mL, single strand ϕX174 was unaffected by the drug, indicating the preference of calicheamicin $\gamma_1{}^I$ for double strand DNA.

Without exception, the preferred site of attack was the 5'C of a TCCT sequence and three nucleotides towards the 3' side of the 3'G in the complementary AGGA box.[7] This asymmetric cleavage pattern to the 3' side on opposite strands indicates interaction of the drug with the minor groove of DNA. This hypothesis is reinforced by a competition experiment with retropsin (which is known to bind in the minor groove) that caused significant alteration of the calicheamicin $\gamma_1{}^I$ cleavage site. Further observations led to the proposal of a cleavage mechanism of the TCCT sites at 5'C (Equation 1).[7]



Eq. 1

Whereas the aglycon is perceived as the "source of latent chemical radiation", the carbohydrate sector is seen to be the DNA recognition device, as shown by Zein *et al.*[12] According to these studies the carbohydrate portion becomes attached to the DNA in such a way that the enediyne core is held in an appropriate position for specific double strand cleavage.

Binding models depicting the calicheamicin-DNA encounter were proposed by two independent groups[8,12,13] and, although the nature of the binding, as well as the source of one of the two hydrogens abstracted by the diyl moiety, are different in each model, both models involve an association between DNA and the thiobenzoate as well as the carbohydrate moiety# by a combination of hydrophobic, electrostatic and hydrogen-bonding interactions.

According to Zein *et al.*,[12] this association then guides the enediyne moiety into the duplex DNA groove at sites where the local helix characteristics (such as groove width and angles) are favorable for the insertion. The movement of the enediyne unit within the groove is then controlled by the carbohydrate-thiobenzoate tail of calicheamicin $\gamma_1{}^{I}$ molecule.

In the presence of thiols, the diradical species then forms in the groove at sites such as TCCT/AGGA, where the spatial orientations are optimal. The diradical abstracts both hydrogens it requires from the sugars (one on each strand) and this initiates DNA double-strand scission. The recognition is not entirely specific and, therefore, when and if the diradical forms in a site on the DNA that is too "wide" and where the hydrogens on the deoxyribose sugars are not accessible, then it abstracts hydrogens from only one strand (as in a mismatch) or from thiol/solvent (as in the case of an unfavored site).

# For NMR studies leading to the conclusion that the carbohydrate tail would be a good binder, see reference 14.

(B) REQUIREMENTS FOR TRIGGERING THE BERGMAN REARRANGEMENT

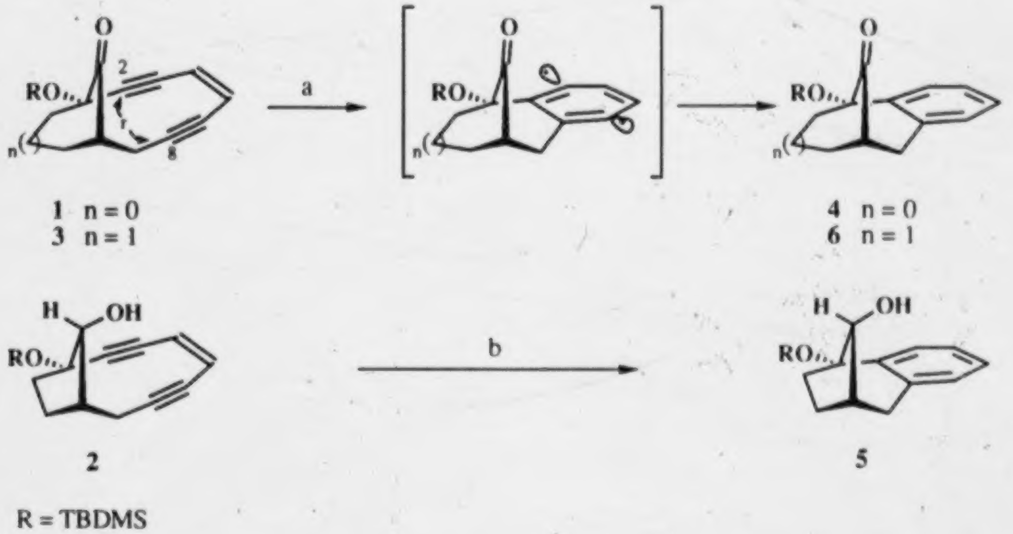
Inspired by the striking capacity of esperamicin/calicheamicin to induce DNA strand scission via a diradical species, researchers have initiated programs directed towards the design and evaluation of simple structures that might mimic[15] the biological action of the natural drugs. Concomitantly, studies were undertaken in order to try to understand the factors controlling biradical formation.

In work aimed at defining those factors, Nicolaou *et al.*[16] gathered information on cyclic conjugated enediynes related to calicheamicin. MM2 calculations on the model compounds, which were either already known or had to be synthesized, led to the conclusion that the distance between the two carbons of the acetylene units was the determining factor in controlling the ease with which the Bergman cyclization takes place. Indeed, in cases where the distance was > 3.35 Å the enediyne could be isolated and was stable at 25 °C, whereas in cases where the distance was < 3.20 Å the compounds were not isolated but were only claimed as transient intermediates, suffering spontaneous cyclization to benzenoid systems. Therefore, the crucial turning point from stability to spontaneous cyclization is in the range of 3.31--3.20 Å.

Alternatively, Magnus *et al.*[17] proposed that the driving force controlling spontaneous cyclization is not the distance but the overall change in strain energy between enediyne and cycloaromatized adduct.

This conclusion is supported by computational evidence[18] and by quantitative experimental and theoretical data. Indeed, in the case of **1** where n = 0 (Scheme 2), even though the separation (r) between C-2 and C-8 is 3.368 Å (vs 3.391 for n = 1), which is in the range postulated for ambient cycloaromatization (< 3.35 Å), the compound is very resistant to closure. It undergoes cycloaromatization 650 times more slowly at 124 °C than its higher homologue **3**. Moreover, the cycloaromatization rate of alcohol **2** (which is more strain-free than its parent ketone) is 216 times faster than that of the ketone and 0.33 times the rate for **3**, with n = 1.

SCHEME 2

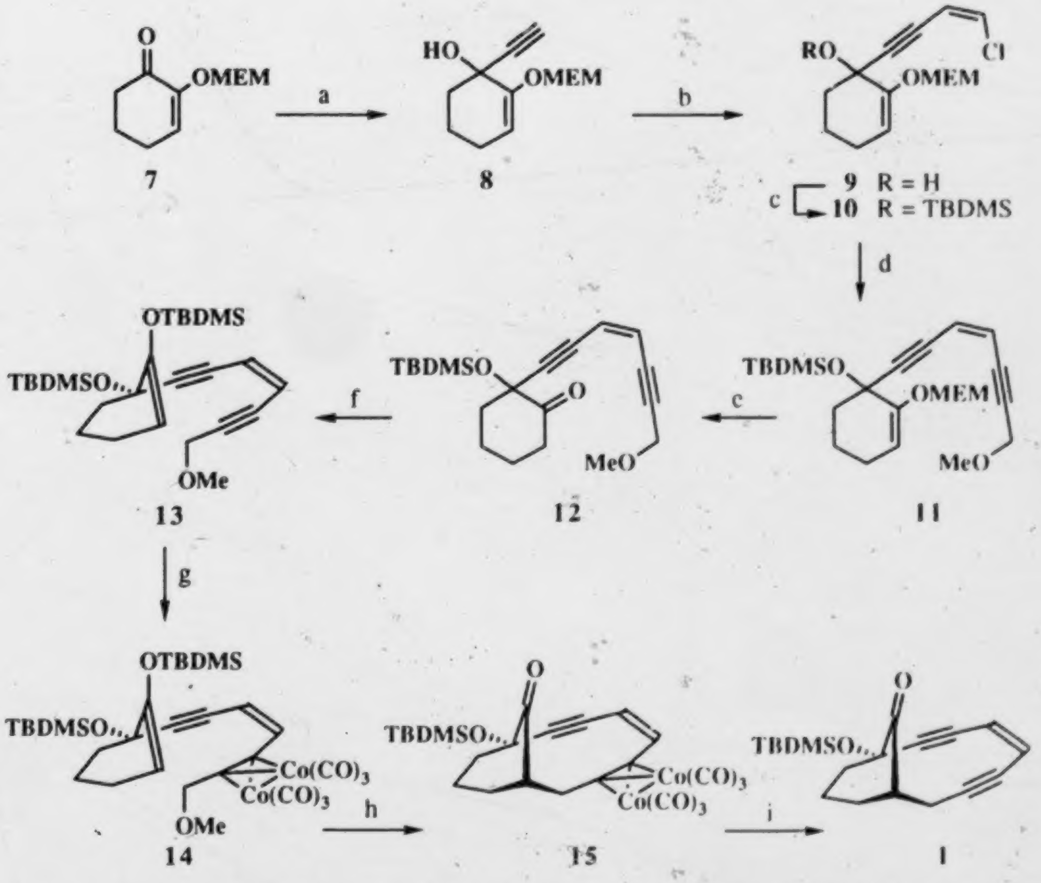


Scheme 2. Reagents and conditions: (a) 1,4-cyclohexadiene, 124 °C; (b) 1,4-cyclohexadiene, 84 °C.

It will be noticed that cycloaromatization was performed by heating a solution of **1-3** in 1,4-cyclohexadiene. Under these conditions, the former are converted into their corresponding benzenediyl derivatives which abstract two hydrogens from cyclohexadiene to produce **4**-**6**.

Compound **1** was synthesized as outlined below (Scheme 3).[19]

SCHEME 3


O
OMEM
7
a
HO
OMEM
8
b
RO
Cl
OMEM
9 R = H
10 R = TBDMS
c
d
TBDMSO
OMEM
MeO
11
e
TBDMSO
O
MeO
12
f
OTBDMS
TBDMSO
OMe
13
g
OTBDMS
TBDMSO
Co(CO)3
Co(CO)3
OMe
14
h
O
TBDMSO
Co(CO)3
Co(CO)3
15
i
O
TBDMSO
1

Scheme 3. Reagents and conditions: (a) lithium acetylide ethylenediamine complex, dioxane, 74%; (b) (Z)-dichloroethylene, $Pd(PPh_3)_4$, CuI, $BuNH_2$, 89%; (c) *tert*-$BuMe_2SiOTf$, Et_3N, CH_2Cl_2, 70%; (d) methyl propargyl ether, $Pd(PPh_3)_4$, CuI, $BuNH_2$, 88%; (e) Me_2BBr, -35 °C, 99%; (f) *tert*-$BuMe_2SiOTf$, Et_3N, 94%; (g) $Co_2(CO)_8$, heptane, 90%; (h) $TiCl_4$ (3.0 equiv), DABCO (1.0 equiv), -43 °C to -35 °C, 50%; (i) I_2, PhH, 70%.

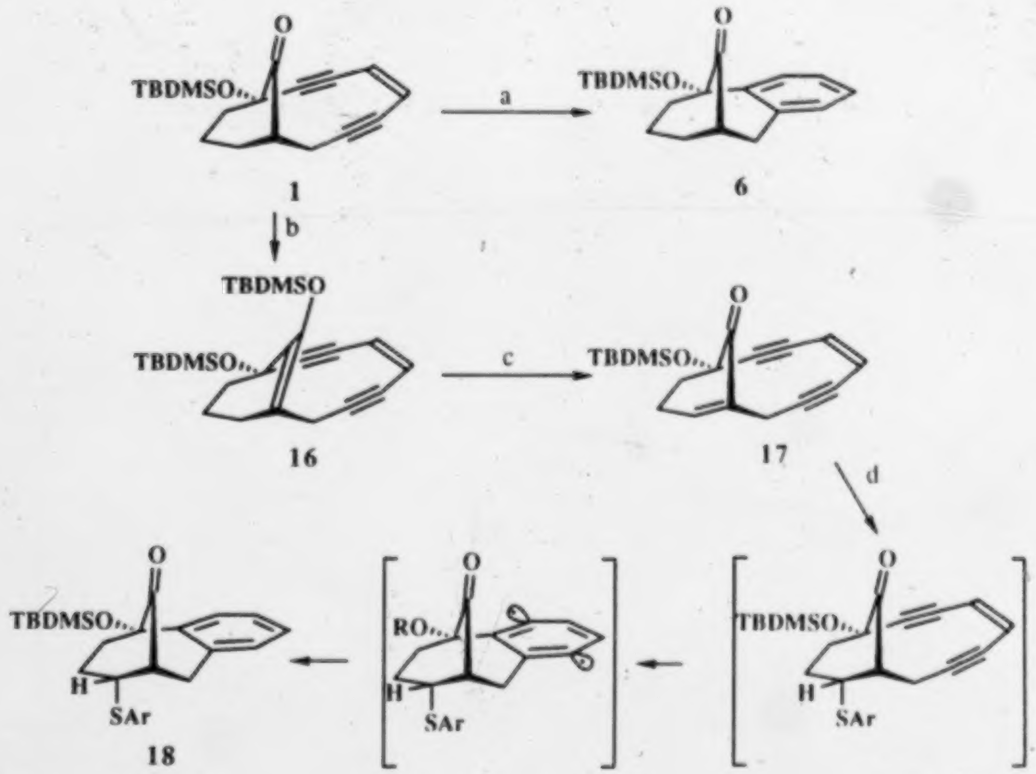
Treatment of cyclohexane-1,2-dione with sodium hydride and methoxymethyl chloride gave **7**, which was exposed to lithium acetylide/ethylenediamine complex in dioxane to give **8**. Palladium mediated coupling of **8** with (Z)-dichloroethylene led to the enyne **9**, and this was converted into silyl ether **10**. A second palladium-mediated coupling of **10**, this time with methyl propargyl ether, introduced the missing acetylene moiety and gave **11**. Conversion of the enolether **11** to the silyl enol ether **13** and protection of one acetylene [dicobalt octacarbonyl/heptane] gave dicobalt hexacarbonyl adduct **14** (80% from **11**). Formation of the dicobalt hexacarbonyl is necessary in order to avoid premature Bergman cycloaromatization. Pettit-Nicholas reaction on **14** generated the bicyclic compound **15** (50%) as a crystalline material, and finally, decomplexation with iodine afforded the target 13-ketobicyclo[7.3.1]diyene **1** as a reasonably stable compound.#

As stated previously, in the biological aspects section (page 124), an intramolecular thiolate addition to C-9 changes the hybridization from sp^2 to sp^3, and this in turn triggers the cycloaromatization. The fact that such a process could be triggered intermolecularly by addition of thiols to C-10 was demonstrated by Magnus on model **17** (Scheme 4).[21]

Treatment of **1** with potassium hexamethyldisylazide and silylation, gave the bridgehead enol ether **16** (89%). When **16** was treated with phenylselenyl chloride followed by hydrogen peroxide, the bridgehead enone **17** was isolated in 83% yield.

# For an example of a very similar synthesis of **1**, followed by cycloaromatization in carbon tetrachloride to give a dichlorobenzene analog of **6**, see reference 20.

SCHEME 4

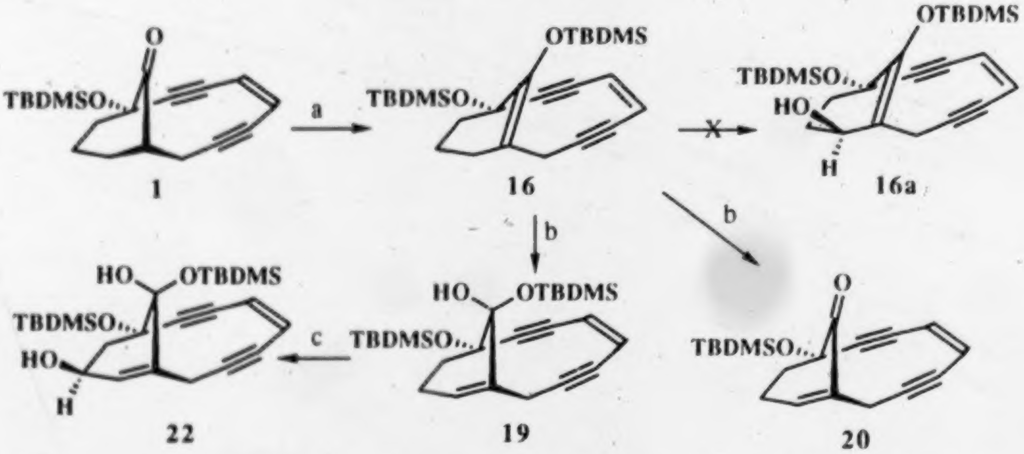

O
TBDMSO
a
O
TBDMSO
1
6
b
TBDMSO
TBDMSO
c
O
TBDMSO
16
17
d
O
TBDMSO
H
SAr
18
O
RO
H
SAr
O
TBDMSO
H
SAr

Scheme 4. Reagents and conditions: (a) 1,4-cyclohexadiene, 84 °C; (b) KHMDS, TBDMSOTf, 89%; (c) PhSeCl; then H_2O_2, 83%; (d) 1,4-cyclohexadiene, 4-chlorothiophenol, *N*-methylmorpholine, 110 °C, 50%.

Compound **17** is a stable compound relative to **1**. It should be noted that the structures assigned to **16** and **17** do not violate Bredt's rule. Heating a mixture of **1** and **17** in 1,4-cyclohexadiene at 80 °C converted **1** into **6**, but left **17** unchanged. However, heating **17** at 110 °C in 1,4-cyclohexadiene in the presence of 4-chlorothiophenol and *N*-methylmorpholine gave the aromatized adduct **18**.

In another investigation, aimed at determining the types of transformation that can be carried out on this system, unexpected results involving selenium dioxide oxidation were obtained.[22] On the basis of the Sharpless mechanism for allylic oxidation of alkenes using selenium dioxide, it was expected that **16** would give **16a** (Scheme 5).

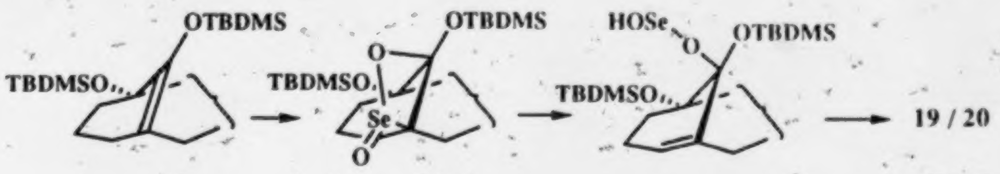
SCHEME 5


O
TBDMSO
1
a
OTBDMS
TBDMSO
16
OTBDMS
TBDMSO
HO
H
16a
b
b
HO
OTBDMS
TBDMSO
HO
H
22
c
HO
OTBDMS
TBDMSO
19
O
TBDMSO
20

Scheme 5. Reagents and conditions: (a) KHMDS, TBDMSOTf, THF, -78 °C, 89%; (b) SeO_2 (1.1 equiv), dioxane, 25 °C, 3 h, **19** (53%) and **20** (14%); (c) SeO_2, 40–50 °C, 90 h, **22** (52%) plus recovered **19** (23%).

Silylation of ketone **1** with gave the desired enol ether **16** (90%) and, when **16** was exposed to SeO_2, the major isolated compound was not **16a** but the hemiketal **19** (53%) along with **20** (14%).

A plausible explanation for the observed products is shown in Equation 2. Electrophilic substitution by selenium dioxide at the bridgehead (C-9) leads to a α-seleno derivative, which can close to the selenooxetane **21** and the latter can collapse by elimination to give **19** and **20**. Further exposure of **19** to selenium dioxide gave the crystalline diol **22** (52%) (Scheme 5).



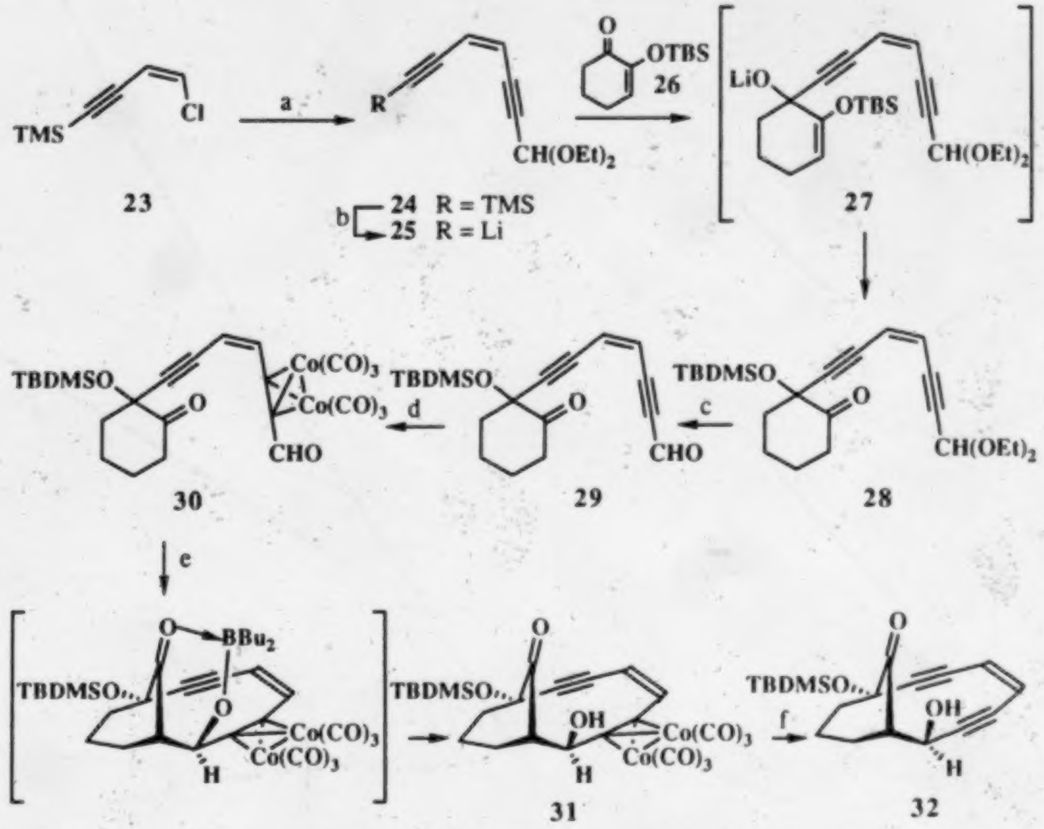
16 **21** Eq. 2

(C) SYNTHESES RELATED TO CALICHEAMICINONE

In work towards the synthesis of the central core of calicheamicin $\gamma_1{}^I$, Magnus *et al.* used a strategy that involved only slight modification of the route followed in the synthesis of model compounds. This modification requires the use of an aldol reaction to generate the bicyclic diynene core and introduce a hydroxyl group at C-8 (with the correct stereochemistry). This C-8 hydroxyl is present in calicheamicin but was absent in the previous models.[23]

The synthesis of **32** (Scheme 6) was achieved utilizing a modification of the route reported by Kadow,[24] which, in turn, is an adaptation of the original sequence developed by Magnus.[19] Basically, the modification involves constructing the whole enediyne unit before (as opposed to after) the coupling with ketone **26** is performed. Palladium coupling of eneyne **23** with acetylene carboxaldehyde diethyl acetal gave the enediyne **24** (68%). Removal of the trimethylsilyl group and treatment of the terminal acetylene with lithium bis(trimethylsilyl)amide generated the lithio derivative **25**, which was quenched with ketone **26** to produce **27**. The latter undergoes silyl migration, thereby providing **28** in good yield (70%).

SCHEME 6

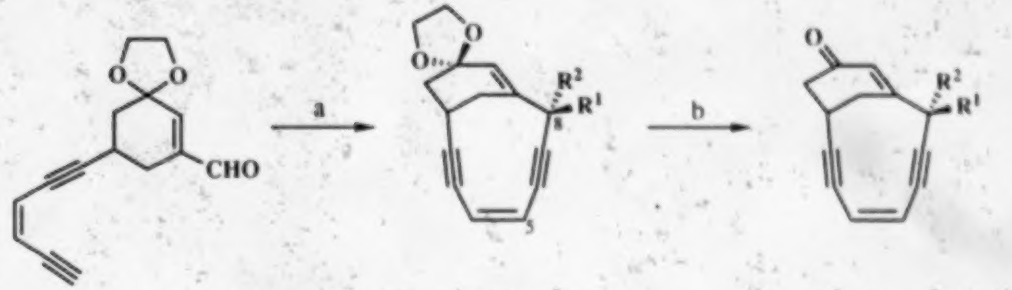

TMS
Cl
23
a
R
CH(OEt)₂
b
24 R = TMS
25 R = Li
O
OTBS
26
LiO
OTBS
CH(OEt)₂
27
TBDMSO
O
CH(OEt)₂
28
c
CHO
29
d
Co(CO)₃
Co(CO)₃
30
e
BBu₂
OH
H
31
f
32

Scheme 6. Reagents and conditions: (a) $HC{\equiv}CH(OEt)_2$, $Pd(PPh_3)_4$, CuI, n-$BuNH_2$, 68%; (b) LiOH, aqueous THF; then LiHMDS, THF, -78 °C, then **26**, 70%; (c) TFA, $CHCl_3/H_2O$, 80%; (d) $Co_2(CO)_8$, 90%; (e) *n*-Bu_2BOTf, DABCO, Et_3N, CH_2Cl_2/THF, 45%; (f) *N*-methylmorpholine *N*-oxide, THF/*t*-BuOH, 25 °C, 76%.

Hydrolysis of diethoxy acetal **28** then gave aldehyde **29**, and the less sterically hindered triple bond was selectively protected as the dicobalthexacarbonyl-adduct **30** . Treatment of **30** with *n*-Bu_2BOTf/amine base resulted in an aldol reaction mediated by a boron enolate, and gave rise to the 12β-hydroxybicyclo[7.3.1]diynene/dicobalt hexacarbonyl adduct **31**. Deprotection of the triple bond proceeded smoothly (*N*-methylmorpholine *N*-oxide) to afford the isolable diynene **32**.

A different approach leading to a calicheamicin deoxyaglycon model was reported by Kende *et al.*[25] The key step involves reaction of enediyne aldehyde **44** with lithium hexamethyldisylazide so as to bring about an intramolecular acetylide cyclization to epimeric carbinols **45a** and **45b** (Scheme 7).

SCHEME 7



44

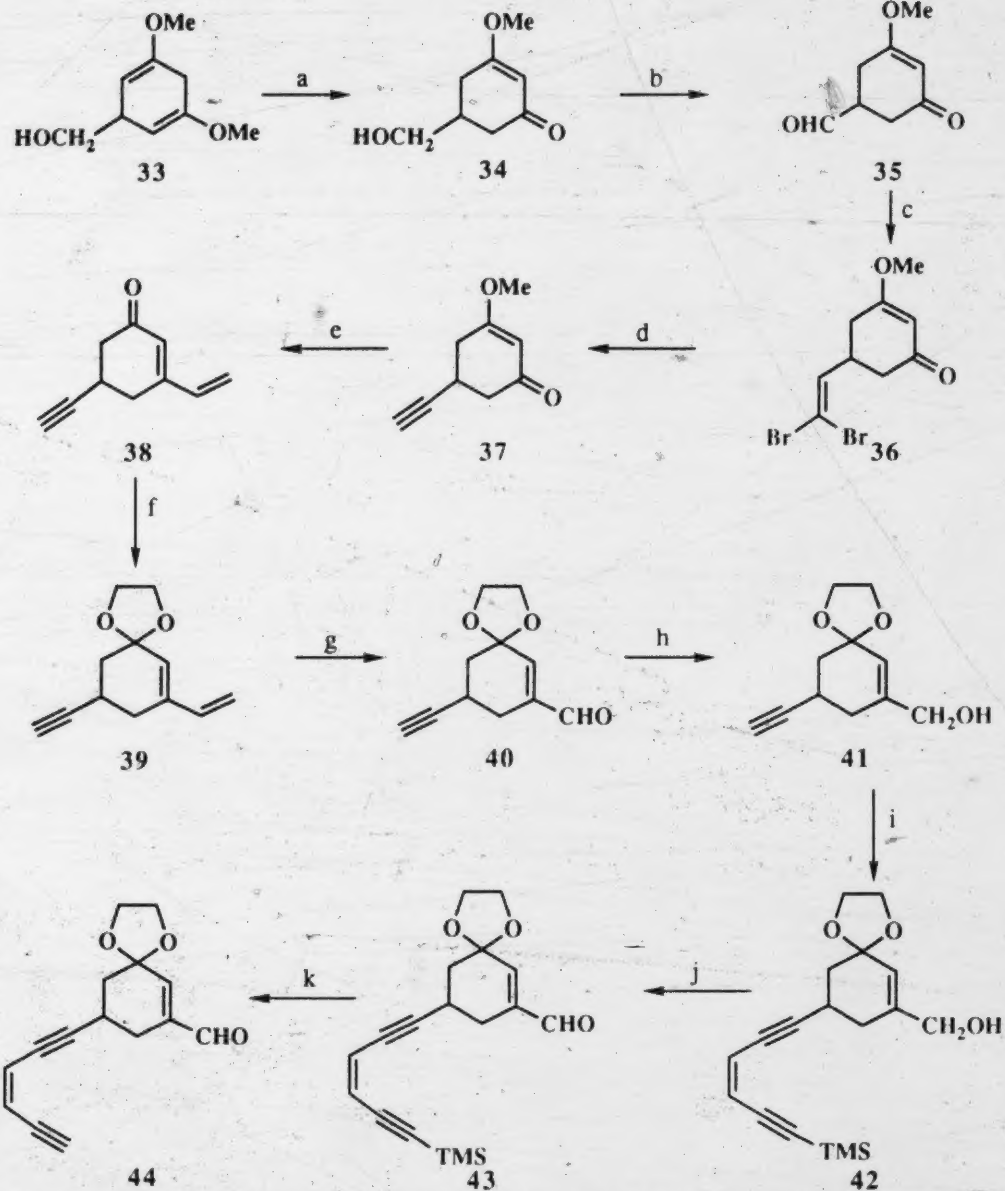
45a $R^1 = H$, $R^2 = OH$
45b $R^1 = OH$, $R^2 = H$

46a $R^1 = H$, $R^2 = OH$
46b $R^1 = OH$, $R^2 = H$

Scheme 7. Reagents and conditions: (a) inverse addition of **44**, $LiN(TMS)_2$, THF; 42% total yield (based on 30% recovered **44**), **45a**:**45b**::3:1; (b) 0.2 M HCl, aqueous acetone, 90%.

Hydrolysis of the known 3,5-dimethoxy-1,4-dihydroxybenzyl alcohol **33** (Scheme 8) gave the β-methoxyenone **34** (63%) and Swern oxidation transformed **34** into aldehyde **35**. This was converted (carbon tetrabromide, triphenylphosphine) into dibromoolefin **36**. At that stage, protection of the carbonyl group in **36** as its enolate, followed by addition of *n*-butyl lithium afforded, after work-up, the acetylene **37** (76%). Addition of vinylmagnesium bromide at 0 °C, and quenching with dilute hydrochloric acid gave the conjugated dienone **38** (91%). To stabilize subsequent intermediates, dienone **38** was converted to the ketal **39**.

SCHEME 8


OMe
HOCH₂
OMe
33
a
OMe
HOCH₂
O
34
b
OMe
OHC
O
35
c
OMe
Br
Br
36
d
OMe
O
37
e
O
38
f
O
O
39
g
O
O
CHO
40
h
O
O
CH₂OH
41
i
O
O
CH₂OH
TMS
42
j
O
O
CHO
TMS
43
k
O
O
CHO
44

Scheme 8. Reagents and conditions: (a) Dowex 50W-X8, MeOH, 63%; (b) DMSO, $(COCl)_2$; then Et_3N, CH_2Cl_2, -78 °C; (c) Ph_3P, CBr_4, CH_2Cl_2, 0 °C, 51% from **34**; (d) LDA, 1 h; then *n*-BuLi, 2 equiv, 2 h, THF, -78 °C, 76%; (e) $CH_2CHMgBr$; then 2 N HCl, THF, 0 °C, 91%; (f) PPTS, ethylene glycol, PhH, 80 °C, 61%; (g) OsO_4, NMMO; then $NaIO_4$, aqueous acetone; (h) $NaBH_4$, MeOH, 61% from **39**; (i) (Z)-1-chloro-4-trimethylsilyl-1-buten-3-yne, $Pd(PPh_3)_4$, CuI, *n*-$BuNH_2$, ether, 59%; (j) DMSO, $(COCl)_2$; then Et_3N, CH_2Cl_2, -78 °C; (k) *n*-Bu_4NF, THF, 60% from **42**.

Then, catalytic osmylation, followed by periodate cleavage, produced aldehyde **40** which was reduced to carbinol **41** in 63% overall yield. At this point, Castro-Stephans coupling of the acetylene with (Z)-1-chloro-4-trimethylsilyl-1-buten-3-yne gave the silyl enediyne **42** (59%). This compound was then oxidized under Swern conditions to the aldehyde **43**.

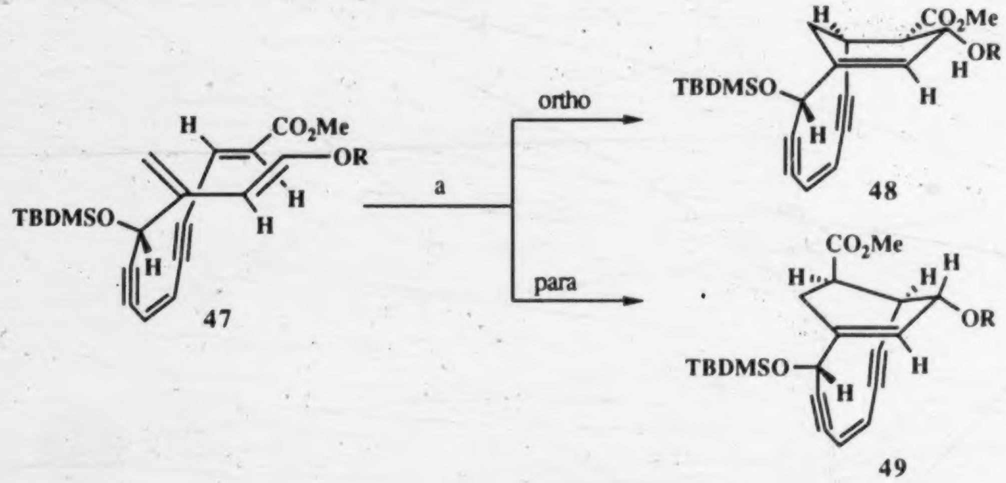
Finally, desilylation produced the key cyclization precursor, the enediyne aldehyde **44**. Inverse addition of **44** to a dilute solution of lithium hexamethyldisilazide in THF, followed by aqueous work-up led to a 3:1 mixture of epimeric cyclized carbinols **45a** and **45b** [42% (based on 30% recovered **44**)] (Scheme 7). Deketalization of the mixture gave the epimeric enones **46a** and **46b** .

The stereochemistry of the major epimer was studied by NOE experiments and shown to be **45a**. On the basis that **45a** did not exhibit long range coupling (> 1.0 Hz for $J_{5,8}$), whereas in both the esperamicins and calicheamicin $\gamma_1{}^{I}$ $J_{5,8}$ is 1.4--2.7 Hz, it was suggested that the C-8 stereochemistry originally assigned for calicheamicin $\gamma_1{}^{I}$ may require revision, and this revision was subsequently made.

A synthesis of a bicyclic core related to the calicheamicin/esperamicin aglycon, using as a key reaction, the skeletal rearrangement of a mesylate derived from a type II Diels-Alder cycloadduct, was reported by Schreiber *et al*. This report[26] solved a problem that had been found in an earlier study by the same group. In that work, the regiochemical outcome (*meta* vs *ortho*) of the type II Diels-Alder cycloaddition leading to the alleged bicyclic core of calicheamicin/esperamicins had been incorrectly assigned.

The initial report[27] suggested that **48** was produced from **47** (Scheme 9). This regiochemistry was in accord with the outcome of other type II Diels-Alder cycloadditions as well as the directing properties of the diene and dienophile substituents. However, in this case, it turned out that *meta* selectivity was favored over *ortho* and so the actual product **49** was not useful for the intended synthesis.

SCHEME 9

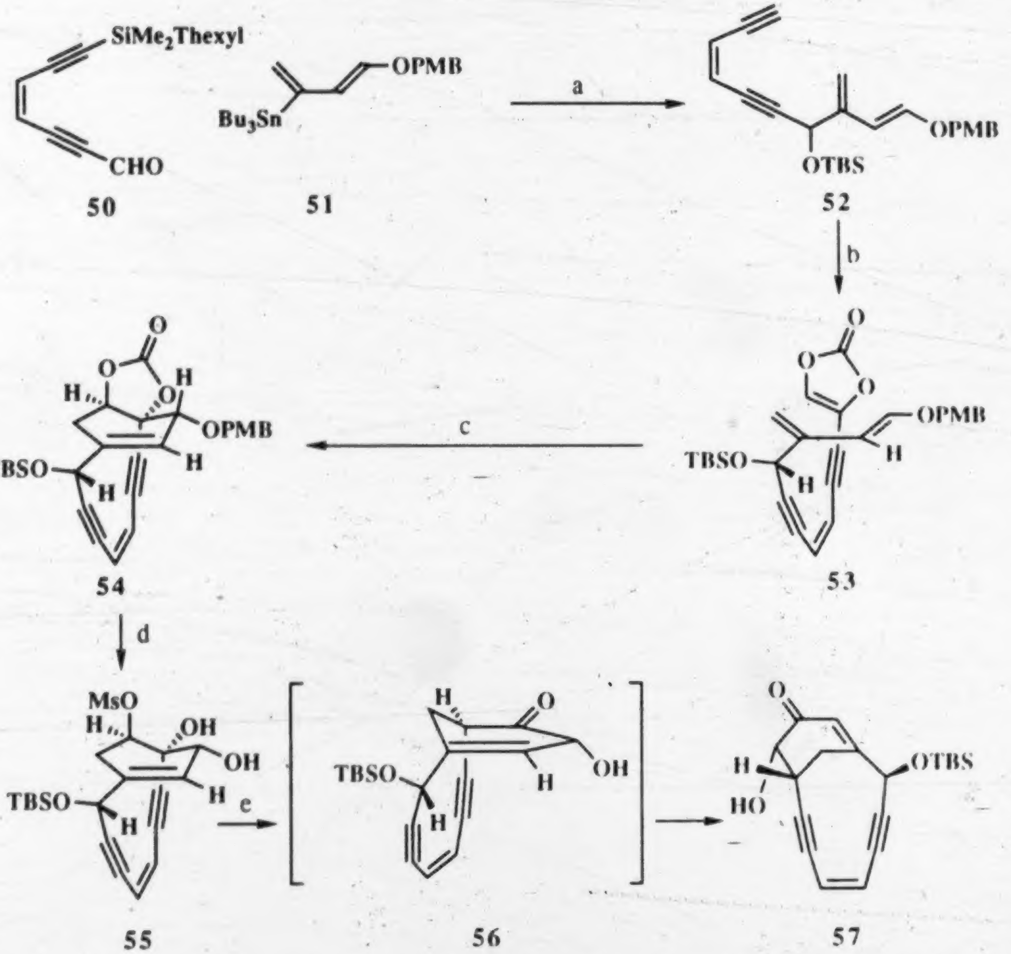

H
CO2Me
OR
TBDMSO
H
H
H
47
a
ortho
para
H
CO2Me
OR
H
TBDMSO
H
H
48
CO2Me
H
H
H
OR
TBDMSO
H
H
49

Scheme 9. Reagents and conditions: (a) hydroquinone, PhH, 80 °C, **49**:**48**::7:1, 75%.

A similar strategy, but one that made use of a carbonate substituent instead of an α,β-unsaturated ester as the diene, was devised in order to solve the problem (Scheme 10).

Aldehyde **50** was prepared by hydrolysis of the corresponding diethoxyacetal which, in turn, was obtained by palladium-catalyzed coupling of (Z)-1,2-dichloroethylene, first with thexyldimethylsilyl acetylene, and then

SCHEME 10


SiMe$_2$Thexyl
CHO
50
Bu$_3$Sn
OPMB
51
a
OTBS
OPMB
52
b
O
O
O
OPMB
TBSO
H
H
53
c
O
O
O
H,,,
O
H
OPMB
TBSO
H
H
54
d
MsO
H,,,
OH
OH
TBSO
H
H
55
e
H
O
TBSO
H
H
OH
56
O
H
HO
OTBS
57

Scheme 10. Reagents and conditions: (a) (i). **51**, n-BuLi, $MgBr_2$, -78 °C; then **50**, 79%. (ii). n-Bu_4NF. (iii). *tert*-$BuMe_2SiOTf$, Et_3N, 80%; (b) bromovinylene carbonate, $Pd(CH_3CN)_2Cl_2$, CuI, Et_3N, PhH, 49%; (c) Kishi's radical inhibitor, PhH, 120 °C, 40%; (d) (i). K_2CO_3, H_2O/MeOH, 83%. (ii). MsCl, 73%. (iii). DDQ, 91%; (e) Et_2AlCl (6 equiv), CH_2Cl_2, -78 °C, 2 h then -78 °C to -20 °C, 2 h, 65%.

with 3,3-diethoxy-1-propyne (60%). The whole process could be achieved without isolation of intermediates. The vinyl stannane **51** was prepared in three steps from 2-butyne-1,4-diol, and coupling of **50** with the vinyl lithium derivative of **51**, followed by desilylation of the acetylene and silylation of the resulting hydroxyl produced **52** (80% overall).

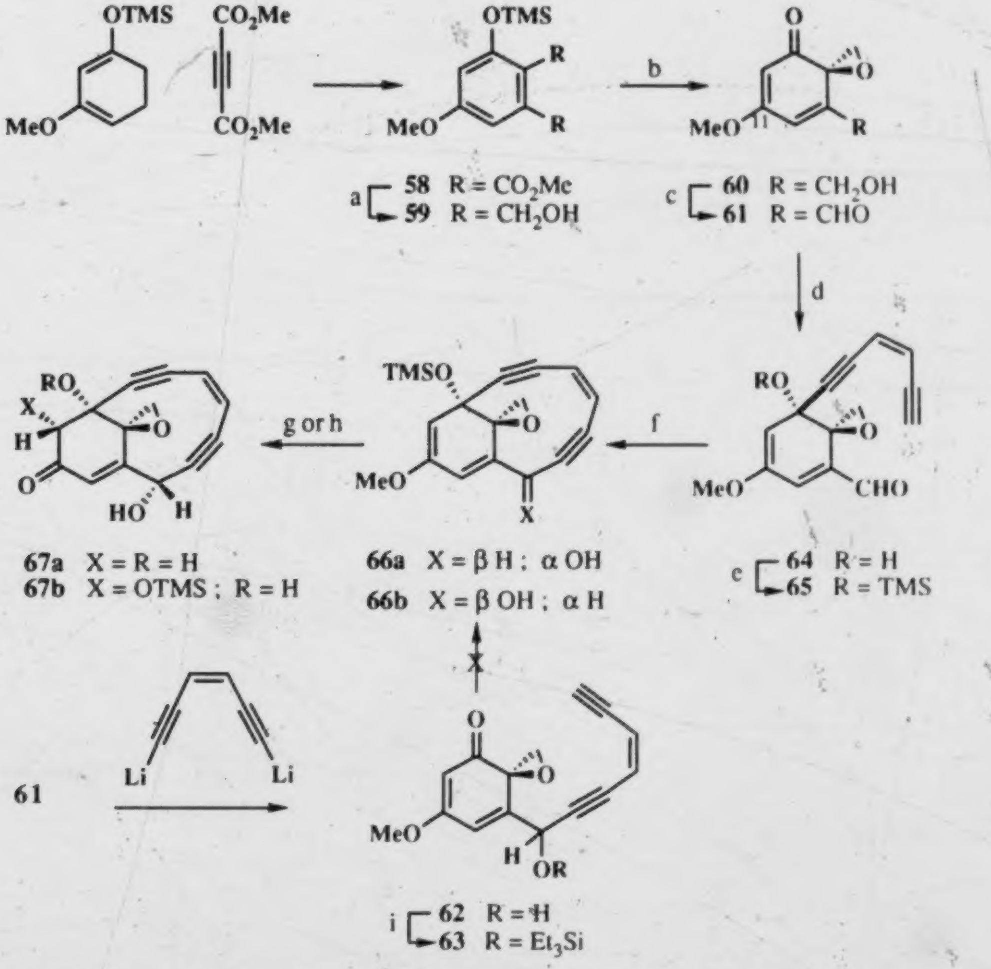
Palladium-mediated coupling of the terminal acetylene portion of **52** with bromovinylene carbonate then gave the cycloaddition precursor **53**. When heated in the presence of Kishi's radical inhibitor, **53** underwent cycloaddition with excellent diastereoselectivity (β/α = 20:1) and the anticipated para bridged regioselectivity to provide **54**. It will be noticed that in the process, the enediyne moiety, which is part of the calicheamicin molecule, has been used as a connector joining the diene and the dienophile and this connection provided a favorable geometric constraint, allowing the cyclization to take place easily.

Saponification of the cyclic carbonate **54**, selective mesylation of the secondary hydroxyl, and removal of the *p*-methoxybenzyl protective group provided the pinacol substrate **55**. Treatment of **55** with diethylaluminium chloride triggered a pinacol rearrangement which, after isomerization of the presumed intermediate **56**, gave the desired enone **57**.

Structure **57** now possess the correct skeleton of the bicyclic core of calicheamicin/esperamicin, but lacks only a hydroxyl group at C-1 (lost in the rearrangement process) and the urethane moiety at C-10.

Danishefsky *et al.* devised a strategy leading in a few steps to an extensively functionalised core.[28] The central element of their approach is the coupling of ketoaldehyde **61** (Scheme 11) with the known (Z)-1,6-dilithiohexa-3-ene-1,5-diyne.

SCHEME 11


OTMS
CO_2Me
MeO
CO_2Me
OTMS
R
MeO
R
b
O
O
MeO
11
R
a
58 R = CO_2Me
59 R = CH_2OH
c
60 R = CH_2OH
61 R = CHO
d
RO
X
H
O
O
HO
H
g or h
TMSO
O
MeO
X
f
RO
O
MeO
CHO
67a X = R = H
67b X = OTMS ; R = H
66a X = β H ; α OH
66b X = β OH ; α H
e
64 R = H
65 R = TMS
61
Li
Li
O
O
MeO
H
OR
i
62 R = H
63 R = Et_3Si

Scheme 11. Reagents and conditions: (a) $LiAlH_4$; (b) $NaIO_4$, aqueous THF, 65% overall; (c) Dess-Martin periodinane, 70%; (d) lithium *N*-methylanilide, THF, -40 °C; then 1,6-dilithiohexa-3-ene-1,5-diyne (2 equiv), -78 °C, 60%; (e) TMSOTf, 70%; (f) $KN(TMS)_2$, PhMe, -78 °C, 52%, **66a**:**66b**::10:1; (g) $(CO_2H)_2$, THF/H_2O, 90%; (h) *m*-CPBA, THF/H_2O, 50%; (i) TESOTf.

Compound **59** (Scheme 11), available by reduction of **58**, was oxidized to **60** using sodium periodate, and reaction of **60** with the Dess-Martin periodinane then gave **61** (70%). At this point, introduction of the enediyne moiety is possible because the carbonyl group at C-11 is protected as methyl enol ether. Monoaddition of the dilithioenediyne to **61**, and conversion of the resulting hydroxyl to its triethylsilyl derivative produced **63**. Interestingly, **63** failed to undergo the desired cyclization to the triethylsilylether derivative of **66a**. Success was achieved, however, by an adaptation of the Commins concept of *in situ* aldehyde protection.. Treatment of the starting ketoaldehyde **61** with lithio *N*-methylanilide generated the lithio α-aminoalkoxide adduct, which was treated with 2 equiv of dilithioenediyne. This procedure gave, after work-up, the mono-adduct **64** (60%) resulting presumably by attack of the acetylide from the less hindered face of **61**. Silylation of the alcohol and deprotonation of the terminal acetylene provided the bicyclic compounds **66a** and **66b** (10:1). Mild acidic hydrolysis or oxidation (*m*-CPBA/THF/water) of **66a** gave **67a** and **67b**, respectively.

It will be noted that **67a** represents a highly functionalised version of the calicheamicin core and that the siloxy ketone **67b** contains the additional oxygen required for esperamicin, though an inversion at C-12 is still required. The spiro-epoxide moiety not only prevents the enone system from aromatizing but will also serve eventually as a handle for elaboration of the chain containing the trisulfide moiety.

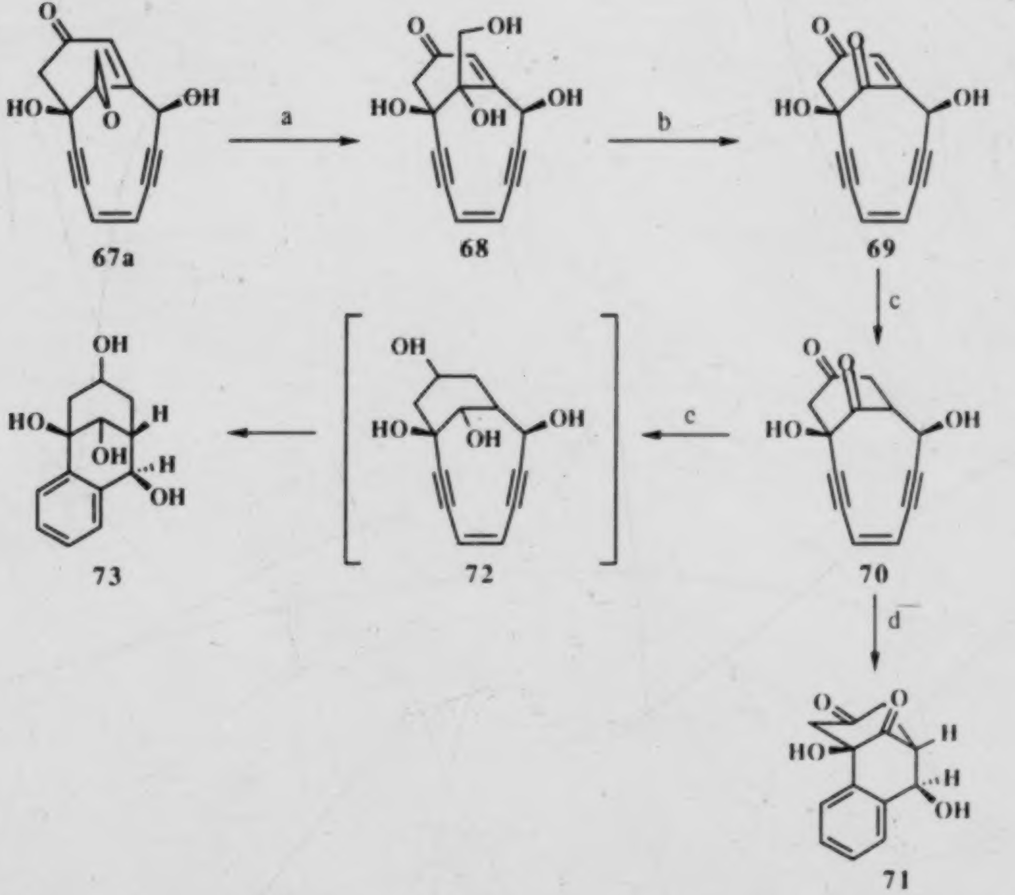
In subsequent studies, attempts to deliver a range of nucleophiles to the bridgehead enone were unsuccessful and therefore, it became clear that in order to saturate the double bond and trigger the Bergman cycloaromatization, modification of the substrate would be necessary.[29]

It was believed that this immunity against nucleophiles was due to steric hindrance by the pseudoaxial substituent at the one-carbon bridge and therefore the spiro-epoxide moiety had to be modified.

Solvolysis of **67a** gave the tetrol **68** which was converted to enedione **69** (Scheme 12). Reaction of **69** with zinc in acetic acid reduced the double bond of the enedione system, thus giving **70**, and thermolysis in the presence of 1,4-cyclohexadiene afforded the cycloadduct **71**. Alternatively, treatment of **70** with sodium borohydride in the presence of 1,4-cyclohexadiene at room temperature gave cycloadduct **73**. Here, reduction of the C-1 bridged ketone is thought to be the major factor responsible for accelerating the cycloaromatization. This interpretation is in keeping with discoveries of Magnus and co-workers in related model systems, where reduction of a ketone to an alcohol at the one-carbon bridge exerted the same effect.[19,30] Both **70** and **72** were shown to effect single and double strand cleavage of ϕX174 form I DNA.

As no intermolecular Michael reaction could be achieved on compound **67a**, an alternative line of attack was sought which would study the feasibility of an intramolecular Michael addition. It was felt at the time that this alternative should work, at least in principle, since such a process is presumably involved in the natural product itself.[31]

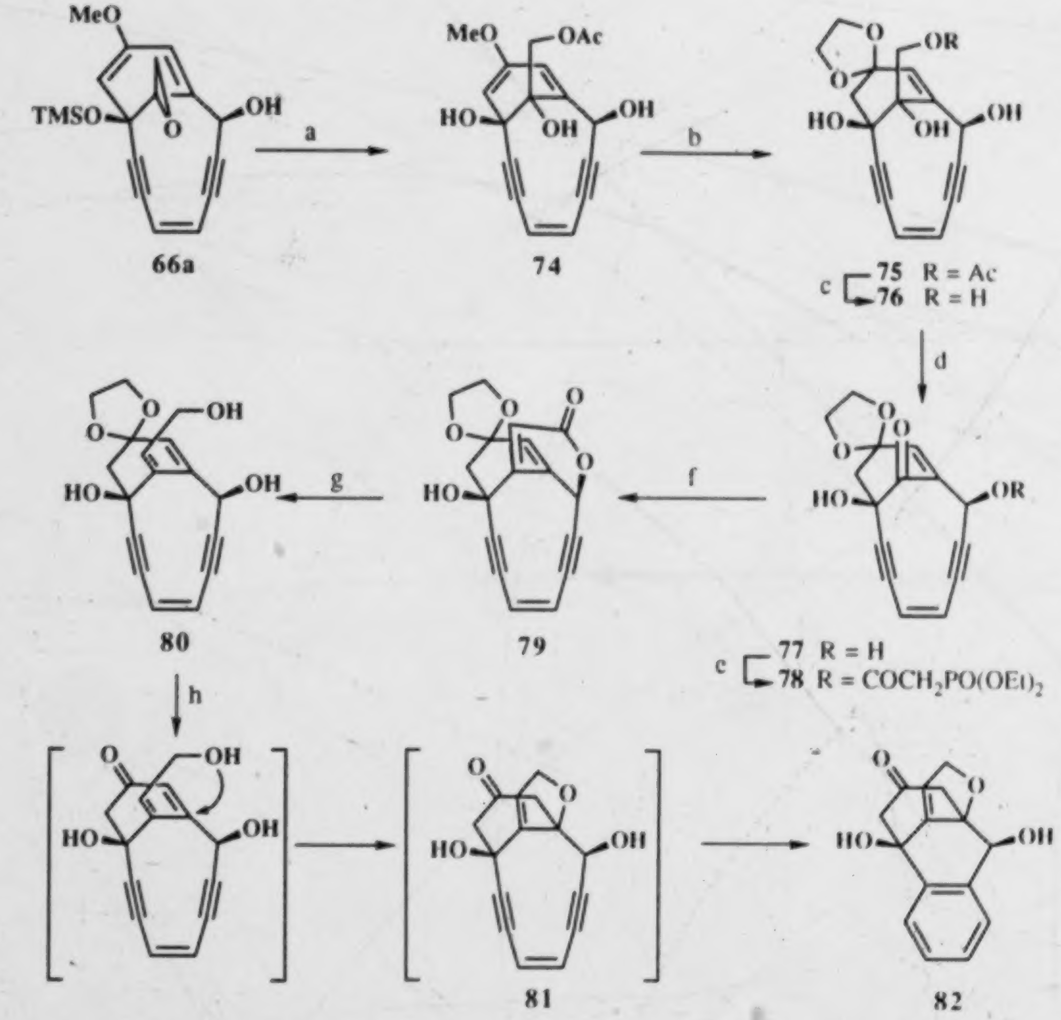
SCHEME 12



Scheme 12. Reagents and conditions: (a) HCO_2NH_4, HCO_2H, THF/H_2O, 65 °C, 80%; (b) H_5IO_6, THF; (c) Zn, AcOH, 82% overall; (d) 1,4-cyclohexadiene, CH_3CN, 82 °C, 6 h, 40%; (e) $NaBH_4$, MeOH, 1,4-cyclohexadiene, 25 °C, 50%.

Careful solvolysis of the previously described spiro-epoxide **66a** (Scheme 13) gave the enol ether **74** which was converted to dioxolane **75**. Deacetylation and cleavage of the diol moiety with periodic acid afforded ketone **77** and then treatment with diethylphosphonylacetic acid and dicyclohexylcarbodiimide produced the monoester **78**.

SCHEME 13


MeO
TMSO
O
OH
66a
a
MeO
OAc
HO
OH
OH
74
b
O
O
OR
HO
OH
OH
c
75 R = Ac
76 R = H
d
O
O
O
HO
OR
c
77 R = H
78 R = COCH₂PO(OEt)₂
f
O
O
O
O
HO
79
g
O
O
OH
HO
OH
80
h
O
OH
HO
OH
O
O
HO
OH
81
O
O
HO
OH
82

Scheme 13. Reagents and conditions: (a) AcOK, AcOH, DMSO, 50 °C; (b) dry ethylene glycol, CSA, 50 °C, 73% from **66a**; (c) NH_3, MeOH; (d) H_5IO_6, THF, 76% from **75**; (e) $(EtO)_2P(O)CH_2CO_2H$, DCC; (f) LiBr, Et_3N, THF, 67% from **77**; (g) DIBAL-H, CH_2Cl_2, -78 °C then $NaBH_4$, MeOH/H_2O, 64%; (h) CSA, 1,4-cyclohexadiene, aqueous THF, 58%.

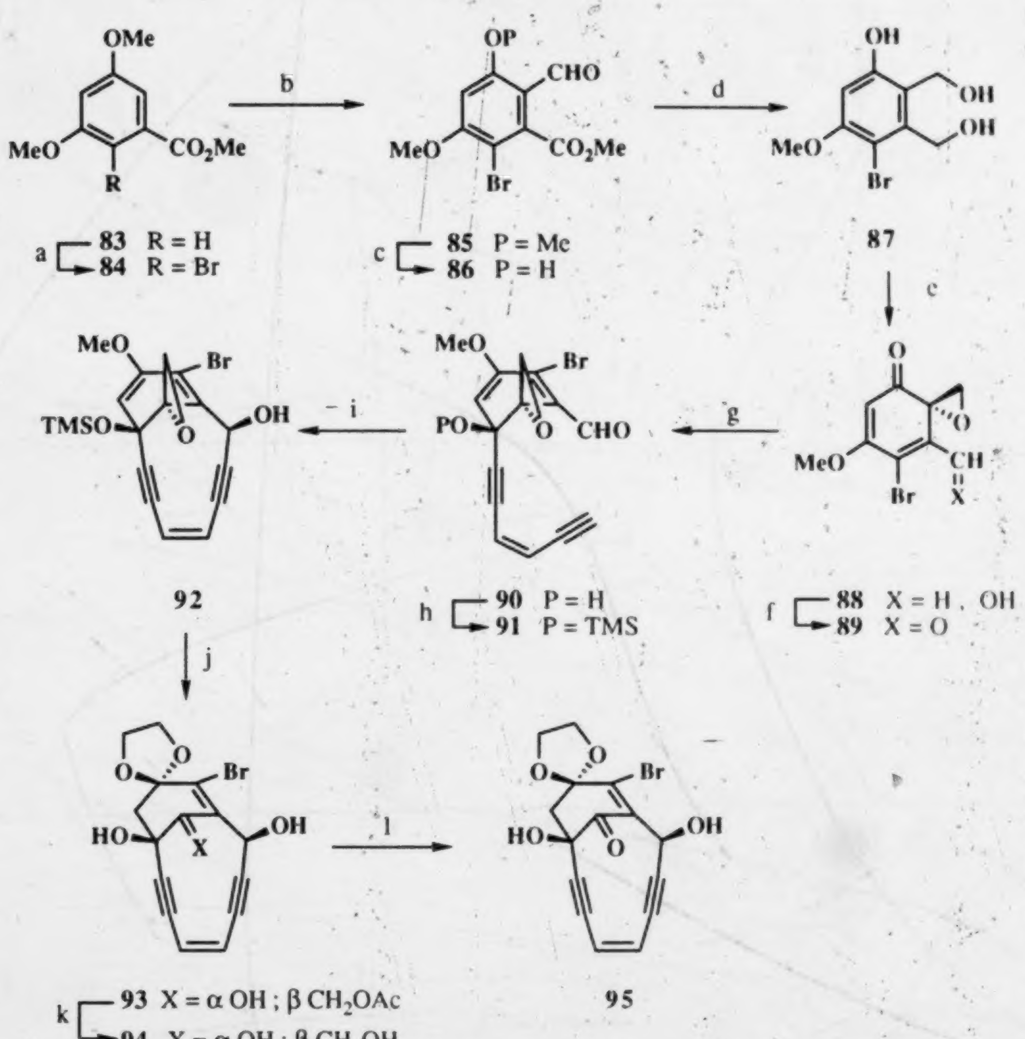
This compound underwent intramolecular Emmons condensation to lactone **79**. It will be noticed that this process introduced the remaining two carbons needed to complete the skeleton and that the hydroxyl group that was esterified served to direct the Emmons condensation. In this way, the double bond at the one-carbon bridge is formed with the correct geometry. Reduction of the lactone moiety of **79** was achieved using diisobutylaluminium hydride followed by sodium borohydride to yield triol **80**.

Treatment of **80** with camphorsulfonic acid in the presence of 1,4-cyclohexadiene gave the dihydrofuran **82** in 58% yield. Presumably, the ketal had cleaved and the resulting enone had then undergone *in situ* Michael addition by the proximal allylic alcohol. The sequence produced **81**, which spontaneously cycloaromatizes. This example clearly shows that a properly placed intramolecular nucleophile is indeed capable of undergoing Michael addition to the enone, and thus triggering the Bergman cyclization.

Finally, Danishefsky *et al.* reported the attainment of the first and only total synthesis of the aglycon portion of calicheamicin in which, as they mention, "a solution [was found] to the problem of the elusive urethane".[32]

The approach was similar to that used earlier on model systems by the same group. However, it was necessary to introduce the urethane function at the bridgehead double bond, and the optimal timing for this installation emerged as a serious problem. Commercially available ester **83** (Scheme 14) underwent regiospecific bromination to **84**, which, upon formylation, gave **85**.

SCHEME 14

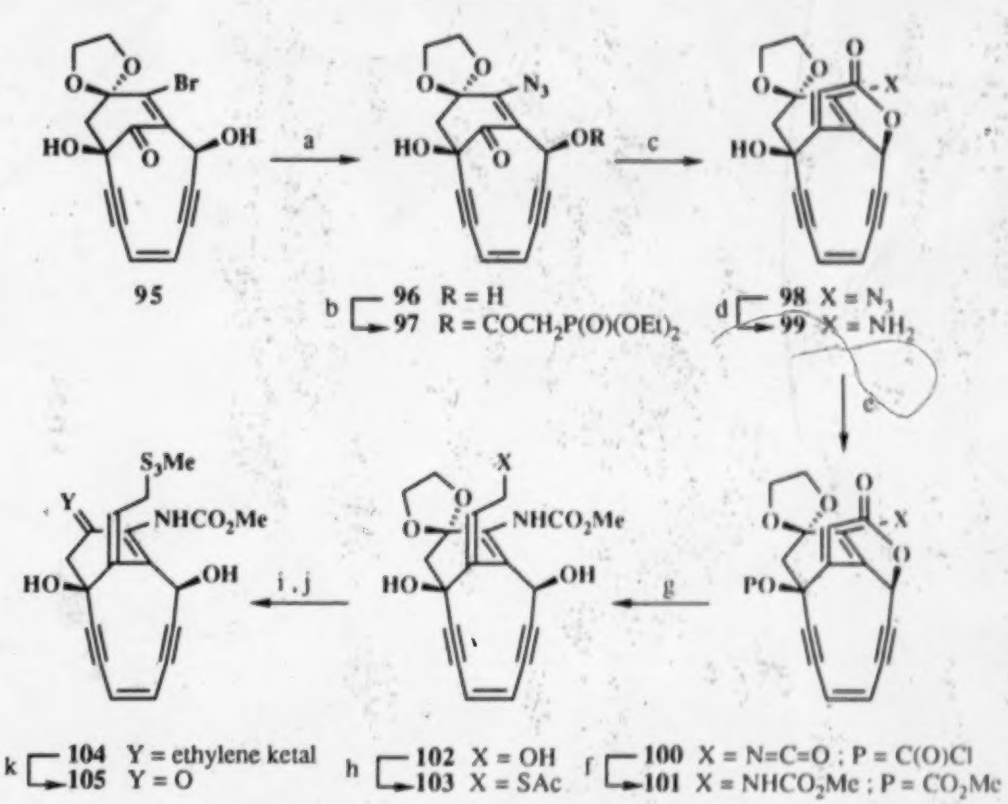

OMe
MeO
CO₂Me
R
b
OP
CHO
MeO
CO₂Me
Br
d
OH
OH
OH
MeO
Br
a
83 R = H
84 R = Br
c
85 P = Me
86 P = H
87
e
MeO
Br
TMSO
O
OH
i
MeO
Br
PO
O
CHO
g
O
O
MeO
CH
Br
X
92
h
90 P = H
91 P = TMS
f
88 X = H, OH
89 X = O
j
O
O
Br
HO
X
OH
l
O
O
Br
HO
O
OH
k
93 X = α OH ; β CH₂OAc
94 X = α OH ; β CH₂OH
95

Scheme 14. Reagents and conditions: (a) NBS, CH_3CN; (b) Cl_2CHOMe, $TiCl_4$; (c) BCl_3; 63% from **83**; (d) DIBAL-H; (e) $NaIO_4$; (f) Dess-Martin periodinane; *ca* 40% from **86**; (g) lithium *N*-methylanilide then dilithioenediyne; (h) TMSOTf; (i) potassium 3-ethyl-3-pentoxide, 40% from **89**; (j) (i)CSA, ethylene glycol, 89%. (ii) AcOK, AcOH, DMSO; (k) NH_3, MeOH; (l) $NaIO_4$; 83% overall.

The aldehyde function was employed to direct regiospecific monodemethylation (by boron trichloride), giving rise to the required phenol **86** (65% from **83**). The sodium salt of **86** was reduced (diisobutylaluminium hydride) to provide an unstable triol **87**, which, upon treatment with sodium periodate, afforded **88**. Oxidation of crude **88** with the Dess-Martin periodinane led to the spiroaldehyde **89** (40% from **86**).

The usual dilithioenediyne was added to the ketone (in the nominal presence of the aldehyde, using the *in situ* protection described previously) to give **90**. Silylation of the tertiary alcohol and cyclization then provided the core system **92** (as a single isomer). Compound **92** was converted to the ketal **93**. Acetolysis of the epoxide, deacetylation and cleavage of the diol moiety gave the ketone-ketal **95** (83% from **93**). At this point, the bridgehead enone is set up for introduction of an azido function. For this to be possible, the ketone at the one-carbon bridge had to provide adequate enolate stabilization to support an addition-elimination mechanism, a possibility presaged by the research of Magnus.[22,32,] Reaction of **95** with sodium azide in methanol afforded **96** (82%). This last step not only introduces the crucial amine moiety necessary for elaboration to the target molecule but provides a very adequate protected form (azide) of the amine (Scheme 15). The alcohol was acylated and the resultant ester **97** subjected to intramolecular Emmons condensation. This operation produced the unsaturated lactone **98** (50% from **96**). The conjugation afforded by the unsaturated lactone provided a sufficiently stable setting for the steps required to transform the azide to the methyl carbamate function.

SCHEME 15

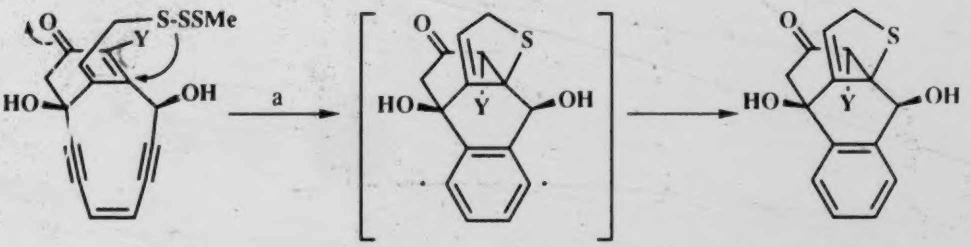

Br
OH
HO
O
95
a
N₃
OR
b
96 R = H
97 R = COCH₂P(O)(OEt)₂
c
X
d
98 X = N₃
99 X = NH₂
e
PO
f
100 X = N=C=O ; P = C(O)Cl
101 X = NHCO₂Me ; P = CO₂Me
g
NHCO₂Me
h
102 X = OH
103 X = SAc
i , j
S₃Me
Y
k
104 Y = ethylene ketal
105 Y = O

Scheme 15. Reagents and conditions: (a) NaN_3, MeOH, 82%; (b) $(EtO)_2P(O)CH_2COCl$, pyridine; (c) LiBr, Et_3N, THF, 50% from **96**; (d) H_2S, piperidine, MeOH, 95%; (e) $(COCl)_2$, pyridine; (f) MeOH, pyridine, 80% overall; (g) DIBAL-H then $NaBH_4$, 43%; (h) CH_3COSH, Ph_3P, DIAD, 45%; (i) DIBAL-H; (j) phtalimidomethyl disulfide, 65% from **103**; (k) CSA, aqueous THF, 65%.

Reduction of **98** (hydrogen sulfide-piperidine-methanol; 95%) led to the fairly robust vinylamine **99**. This compound, upon treatment with phosgene in pyridine, produced the bis acylation product **100**, and thence, upon treatment with methanol in pyridine, to the carbamate-carbonate **101** in 80% overall yield. Treatment of **101** with diisobutylaluminium hydride followed by sodium borohydride, gave the alcohol **102** (43%). The first sulfur atom was introduced by a Mitsunobu reaction on **102** to produce **103**. Deacetylation of **103** and treatment of the crude product with phthalimidomethyl disulfide gave the trisulfide **104** (65% from **103**). Finally the ketal linkage was cleaved and there was obtained *dl*-calicheamicinone **105** as a powder in 65% yield.

When calicheamicinone **105** was treated with benzenethiol, triethylamine and 1,4-cyclohexadiene in methanol for 2 h at room temperatureit was converted into the cycloaromatized tetracycle **107** in 16% yield (Scheme 16).[34] Similarly, **106** afforded **108** in 50% yield.

SCHEME 16



105 Y = $NHCO_2Me$
106 Y = H

107 Y = $NHCO_2Me$
108 Y = H

Scheme 16. Reagents and conditions: (a) BnSH, Et_3N, 1,4-cyclohexadiene, MeOH, 50% **108** from **106**, 16% **107** from **105**.

In summary, the above work represents the first synthesis of calicheamicinone, the clean introduction of the trisulfide trigger, and the thiol-induced cleavage in these systems to initiate the cascade culminating in Bergman cycloaromatization. The urethane functionality is not crucial for the activation cascade, and the thiol used to initiate the cleavage represents a model for the possible involvment of glutathione.

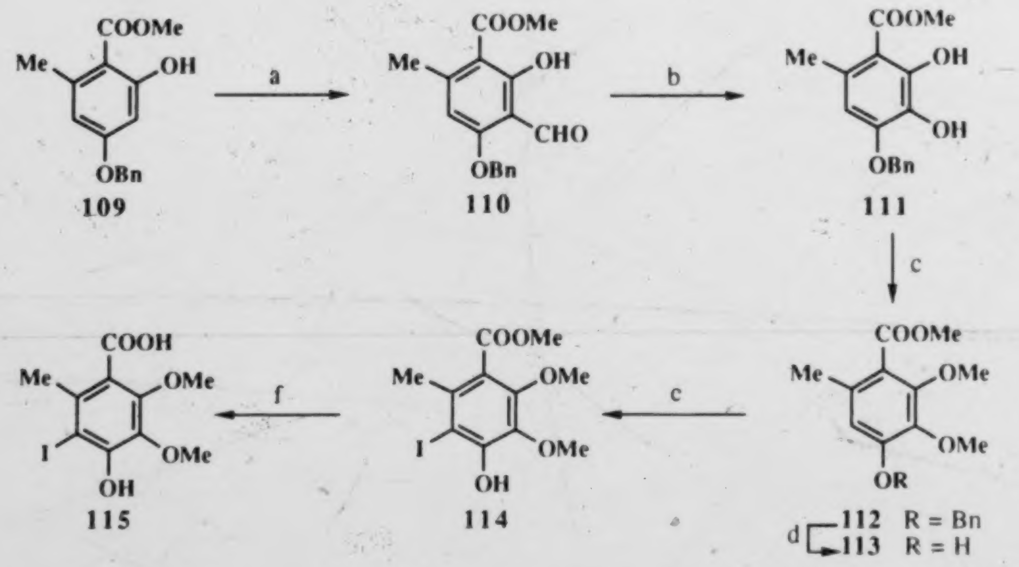
(D) SYNTHESES RELATED TO THE SUGAR PORTION OF CALICHEAMICIN γ_1^I

Even though the main synthetic goal of many organic chemists has been focused on the bicyclic core of calicheamicin, the oligosaccharide fragment of the drug is also being pursued. So far, Nicolaou *et al.* reported the total synthesis of the whole fragment, and the synthesis of three of the five subfragments has been disclosed by Scharf *et al.* The approach disclosed by *Scharf et al.* will be discussed first.

The synthesis of the aromatic ring (ring C) was achieved in six steps (41%) from readily available methyl 4-*O*-benzylorsellinate **109**.[35] Compound **109** was selectively formylated at the 3 position to **110**, and oxidized to phenol **111** by treatment with hydrogen peroxide in alkaline solution (Scheme 17). Methylation gave **112** and the benzyl group was removed by hydrogenolysis. Mild iodination with iodine chloride then yielded **114**, and this compound was demethylated by alkaline hydrolysis to the desired product **115**.

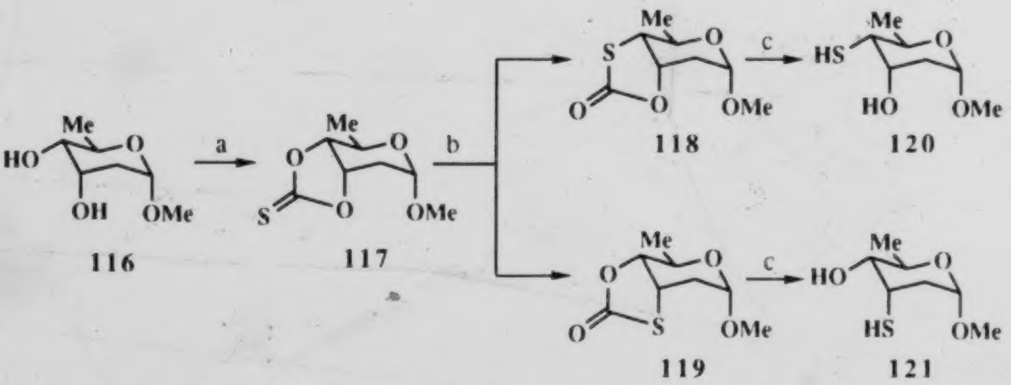
The sulfur containing fragment (ring B) was obtained by a radical-induced rearrangement of a 3,4-thionocarbonate derivative.[36] Methyl 2,6-dideoxy-α-D-ribohexopyranoside **116** was esterified with thiocarbonyldiimidazole and the resulting thiocarbonate **117** was treated with tributyltin hydride and AIBN. The rearranged regioisomeric thiol carbonates **118** and **119** were formed in 31% and 41% yield, respectively (Scheme 18). Alkaline hydrolysis of **118** gave the desired thio sugar **120** as its methyl glycoside.

SCHEME 17


COOMe
Me
OH
OBn
109
a
CHO
110
b
OH
111
c
COOH
OMe
I
115
f
114
OR
112 R = Bn
113 R = H
d

Scheme 17. Reagents and conditions: (a) Cl_2CHOMe, $TiCl_4$, 74%; (b) H_2O_2, aqueous NaOH; 90%; (c) Me_2SO_4, K_2CO_3, acetone; 81%; (d) H_2, Pd, 97%; (e) ICl, CH_2Cl_2, 90%; (f) alkaline hydrolysis.

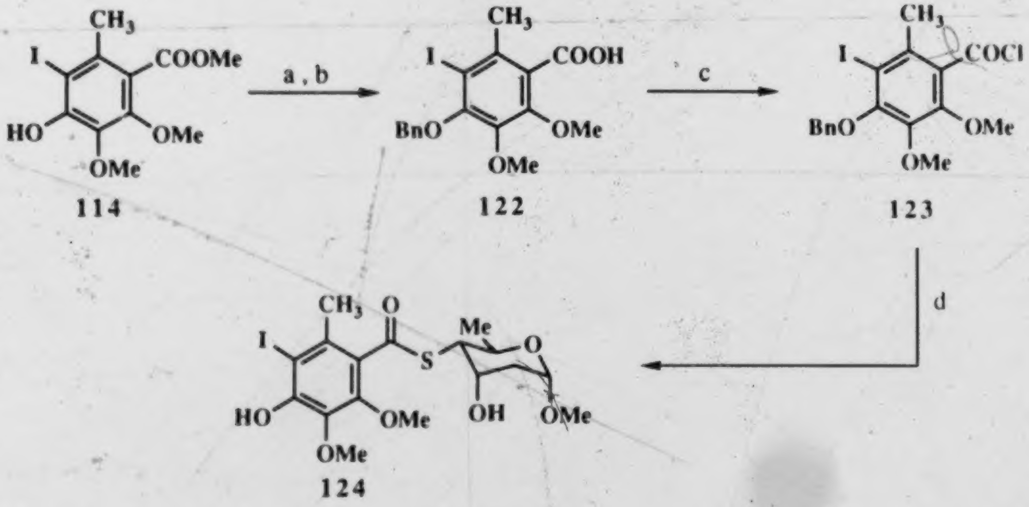
SCHEME 18


Me
HO
O
OH
OMe
116
a
S
117
b
118
c
HS
120
119
121

Scheme 18. Reagents and conditions: (a) thiocarbonyldiimidazole (1.2 equiv), $PhCH_3$, 60 °C, 81%; (b) Bu_3SnH (0.5 equiv), AIBN (1.2 equiv), PhH, 80 °C, 31% of **118** and 41% of **6**; (c) alkaline hydrolysis; 75%.

Coupling of the two subunits (ring B and C) was achieved as follows.[37] Compound **114** was protected as its benzyl ether and the ester was converted to the acid chloride **123** (Scheme 19). Reaction of the thiosugar **120** with **123** in pyridine led to **124** (subunit BC) as a crystalline solid (59%).

SCHEME 19


CH3
I
COOMe
HO
OMe
OMe
114
a , b
CH3
I
COOH
BnO
OMe
OMe
122
c
CH3
I
COCl
BnO
OMe
OMe
123
d
CH3
O
I
S
Me
O
HO
OMe
OH
OMe
OMe
124

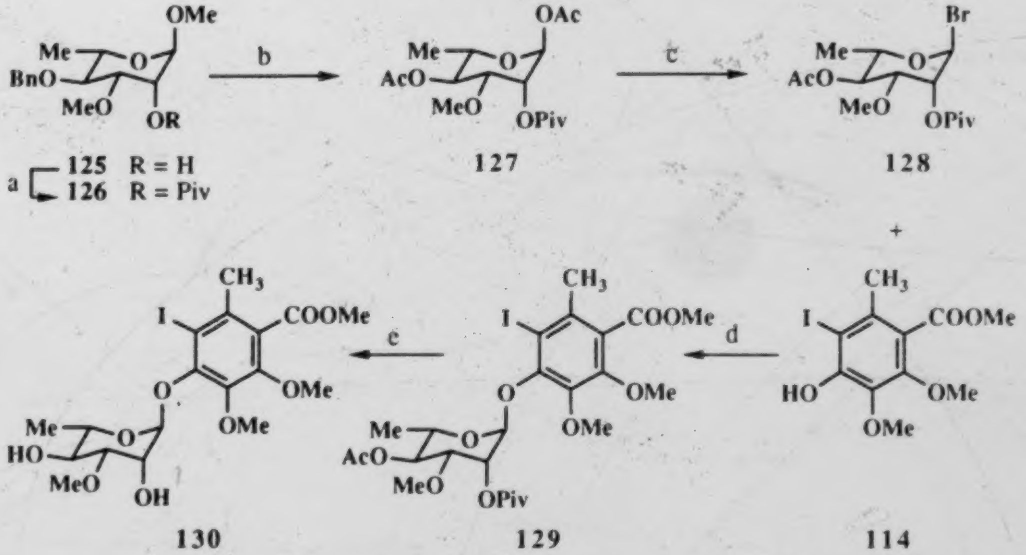
Scheme 19. Reagents and conditions: (a) 1.1 equiv of $PhCH_2Br$, K_2CO_3, acetone, reflux, 92%; (b) 3 equiv of 5 N NaOH, DMSO, 100 °C, 81%; (c) 1.2 equiv of 1-chloro-*N*,*N*,2-trimethyl-1-propenyl-1-amine, CH_2Cl_2, 0–25 °C, 95%; (d) **120**, pyridine, 2 d, 0–25 °C, 59%.

Subunit CD was prepared by coupling of phenol **114** (ring C) with the glycosyl bromide derivative **128** (ring D). Methyl glycoside **125** was treated with pivaloyl chloride to yield **126** (Scheme 20). The pivaloyl residue guarantees the 1,2 *trans* glycosidic coupling and diminishes the formation of by-products in the glycosylation step. Acetolysis gave **127**, which was converted to the glycosyl bromide **128** using hydrogen bromide in acetic acid.

Coupling of **128** with phenol **114**, using silver carbonate on Celite as a catalyst, gave rise to **129** and, finally, cleavage of the ester groups afforded **130** (subunit CD) as a colorless crystalline solid.

This work represents a synthesis of the subunits BC and CD of the olisaccharide fragment of calicheamicin $\gamma_1{}^I$.

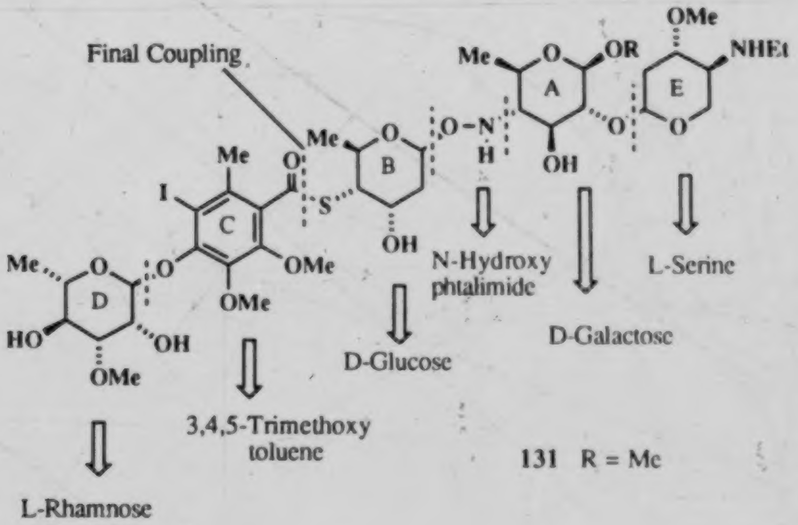
SCHEME 20


OMe
Me
BnO
MeO
OR
O
b
OAc
Me
AcO
MeO
OPiv
c
Br
Me
AcO
MeO
OPiv
125 R = H
a
126 R = Piv
127
128
+
CH3
I
COOMe
HO
OMe
OMe
114
d
CH3
I
COOMe
O
OMe
OMe
Me
AcO
MeO
OPiv
129
e
CH3
I
COOMe
O
OMe
OMe
Me
HO
MeO
OH
130

Scheme 20. Reagents and conditions: (a) PivCl, pyridine, 96%; (b) AcOH, Ac_2O, H_2SO_4 (32/32/1, v/v/v), 98%; (c) HBr, AcOH, CH_2Cl_2, 0–25 °C, 94%; (d) Ag_2CO_3 on Celite, $PhCH_3$, 50 °C, 41%; (e) MeONa, MeOH, 3 d, 52%.

The stereocontroled synthesis of the oligossacharide of calicheamicin $\gamma_1{}^I$ as its methyl glycoside **131**, reported by Nicolaou *et al.*, is based on a novel [3,3]-sigmatropic rearrangement that established the essential elements of ring B and delivered the target molecule in enantiomerically pure form and high overall yield.[38]

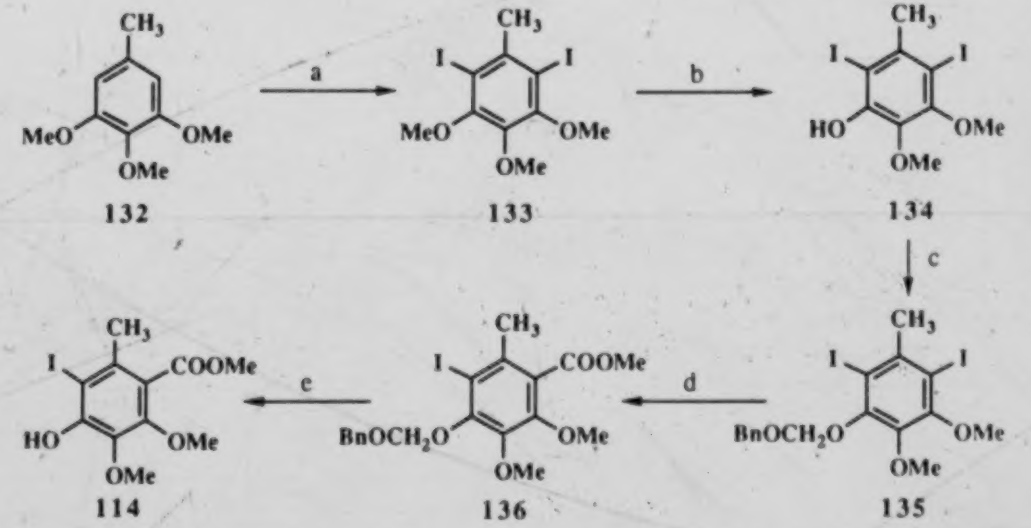
Designated on structure **131** are the strategic bond disconnections that allowed the tracing of the requisite intermediates back to the readily available starting materials. The CO-S linkage was chosen as the key bond for the final coupling reaction.


Final Coupling
Me
I
C
OMe
OMe
O
S
Me
O
B
OH
O
N
H
Me
O
A
OR
OH
O
OMe
E
NHEt
O
Me
O
D
HO
OH
OMe
L-Rhamnose
3,4,5-Trimethoxy toluene
D-Glucose
N-Hydroxy phtalimide
D-Galactose
L-Serine

131 R = Me

The aromatic segment **114** (ring C) was synthesized from 3,4,5-trimethoxytoluene as outlined below.[39] Compound **132** was diiodinated to give **133**, which was monodemethylated to **134** at the less sterically hindered methoxy group, using boron trichloride (Scheme 21). The free hydroxyl group in **134** was protected as the benzyloxymethyl ether **135**. Catalytic methoxycarbonylation of **135** furnished the methyl benzoate **136** as the major product (44% yield, accompanied by *ca* 11% of the regioisomer and 6% of the diester). Finally, removal of the benzyloxymethyl group was achieved under acidic conditions to give **114** (ring C) as a crystalline solid.

SCHEME 21

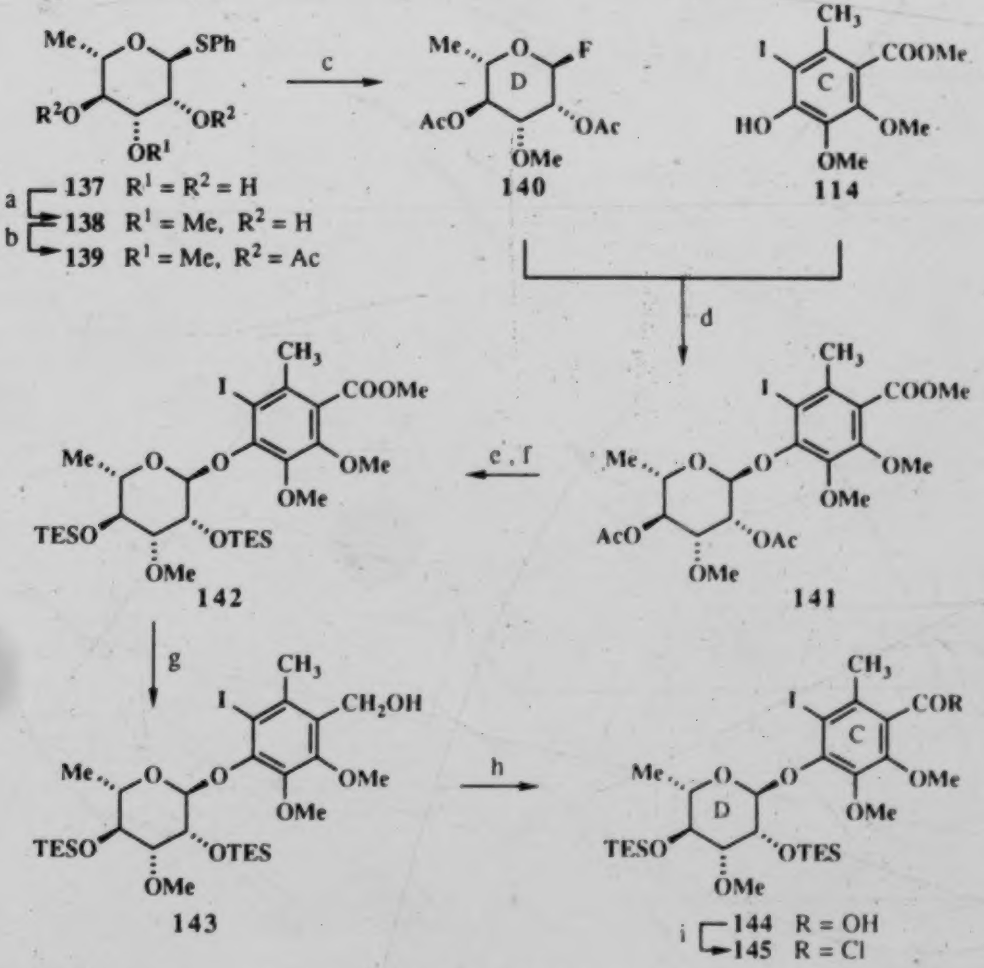


Scheme 21. Reagents and conditions: (a) 1.1 equiv I_2, 0.56 equiv HIO_4, AcOH, 53 °C, 93%; (b) 6.0 equiv of BCl_3, CH_2Cl_2, 58% (plus 13% regioisomer and 12% dihydroxy compound); (c) 1.5 equiv $PhCH_2OCH_2Cl$, 2.0 equiv *i*-Pr_2NEt, $ClCH_2CH_2Cl$, 70 °C, 100%; (d) 0.05 equiv $Pd(OAc)_2$, 0.05 equiv $Ph_2P(CH_2)_3PPh_2$, 2.0 equiv Et_3N, CO atmosphere, DMSO/MeOH (2:1), 70 °C, 44% (plus 11% regioisomer plus 6% dimethyl ester); (e) conc. HCl, MeOH, 89%.

As described below, compound **139** (ring D) was synthesized starting from **137** which, in turn, was made in 60% yield from L-rhamnose, and coupling of **139** with phenol **114** furnished the CD subunit.[40]

Compound **137** (60% yield from L-rhamnose), was selectively methylated at the equatorial 3-hydroxyl group to give **138** (Scheme 22). Acetylation followed by activation of the anomeric position under mild conditions (NBS and DAST) afforded the fluoride **140**, and coupling of **140** (ring D) with phenol **114** (ring C) under the influence of silver perchlorate and tin dichloride gave stereospecifically, glycoside **141** in 80% yield.

SCHEME 22


Me
O
SPh
R²O
OR²
OR¹
a
b
137 R¹ = R² = H
138 R¹ = Me, R² = H
139 R¹ = Me, R² = Ac
c
Me
O
F
D
AcO
OAc
OMe
140
CH₃
I
COOMe
C
HO
OMe
OMe
114
d
CH₃
I
COOMe
Me
O
O
OMe
OMe
TESO
OTES
OMe
142
e, f
CH₃
I
COOMe
Me
O
O
OMe
OMe
AcO
OAc
OMe
141
g
CH₃
I
CH₂OH
Me
O
O
OMe
OMe
TESO
OTES
OMe
143
h
CH₃
I
COR
C
Me
O
D
O
OMe
OMe
TESO
OTES
OMe
i
144 R = OH
145 R = Cl

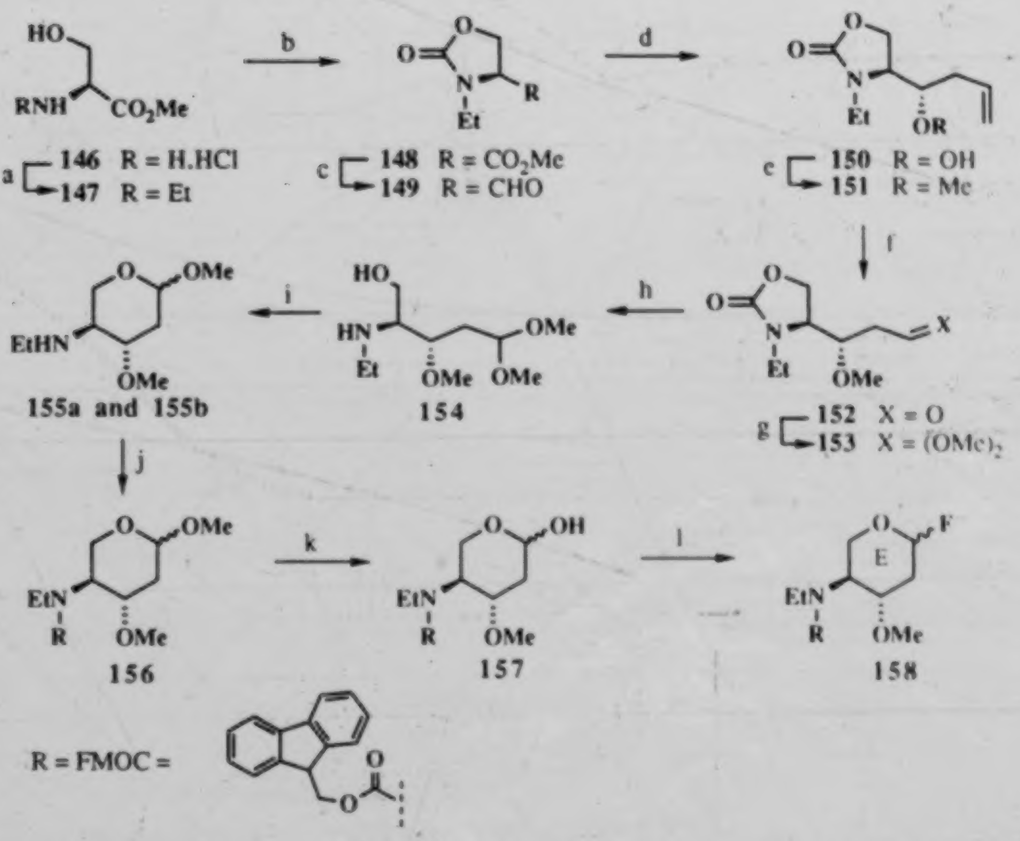
Scheme 22. Reagents and conditions: (a) 1.1 equiv Bu_2SnO, MeOH, 65 °C, then DMF, 4 equiv MeI, 1.1 equiv CsF, 65%, plus 30% starting material **137**; (b) Ac_2O, Et_3N, DMAP cat., CH_2Cl_2, 0–25 °C, 95%; (c) 2.0 equiv DAST, 1.4 equiv NBS, CH_2Cl_2, -78–0 °C, 85%; (d) 1.0 equiv **114**, 2.0 equiv **140**, 4.0 equiv $SnCl_2$, 4.0 equiv $AgClO_4$, 4 Å molecular sieves, CH_2Cl_2, -20–0 °C, 80%; (e) K_2CO_3, MeOH, 100%; (f) TESOTf, 2,6-lutidine, CH_2Cl_2, -20–0 °C, 92%; (g) 2.5 equiv DIBAL-H, CH_2Cl_2, -78–0 °C, 90%; (h) 0.02 equiv. $RuCl_3$ hydrate, 4.0 equiv $NaIO_4$, $CCl_4/MeCN/H_2O$ (2:2:3), 0–25 °C, 75%; (i) $(COCl)_2$, 100% (crude).

Preference for the formation of the α-anomer under these conditions using a variety of fluorides and alcohols had been demonstrated previously.[41] Deacetylation, protection of the free hydroxyl groups and reduction of the ester to the primary alcohol led to **143**. Oxidation to the carboxylic acid **144** and conversion to the acid chloride then afforded the requisite CD subunit **145** in a form suitably set up for eventual coupling with the BAE subunit.

The BAE subunit was synthesized by coupling of a ring B derivative with subunit AE.[38] The synthesis of the two isomers **155a** and **155b** (ring E) proceeded from serine methyl ester hydrochloride **146** (Scheme 23).[40] Reductive alkylation of **146** with acetaldehyde and sodium borohydride produced the ethyl amine **147** (Scheme 23). Oxazolidone formation gave **148** and this was reduced to aldehyde **149** using diisobutylaluminium hydride. Stereoselective addition of an allyl group to the aldehyde function of **149** was achieved *via* the action of (-)-β-methoxydiisopinocampheylborane and allyl magnesium bromide, leading to a single isomer **150** in 75% yield.

This process therefore introduced the carbons needed for elaboration of ring E and produced the chiral center corresponding to C-3 of ring E. Methylation, followed by ozonolysis, led to the methoxy aldehyde **152**, and this was converted to the dimethoxy acetal **153**. Removal of the oxazolidone moiety gave **154** which was cyclized under acidic conditions to the desired ring B derivatives **155a** and **155b**. Protection of the amine (as an FMOC derivative), methyl glucoside hydrolysis, and glycosyl fluoride formation gave **158** (ring E). The compound is properly set up for linkage to a ring A derivative.

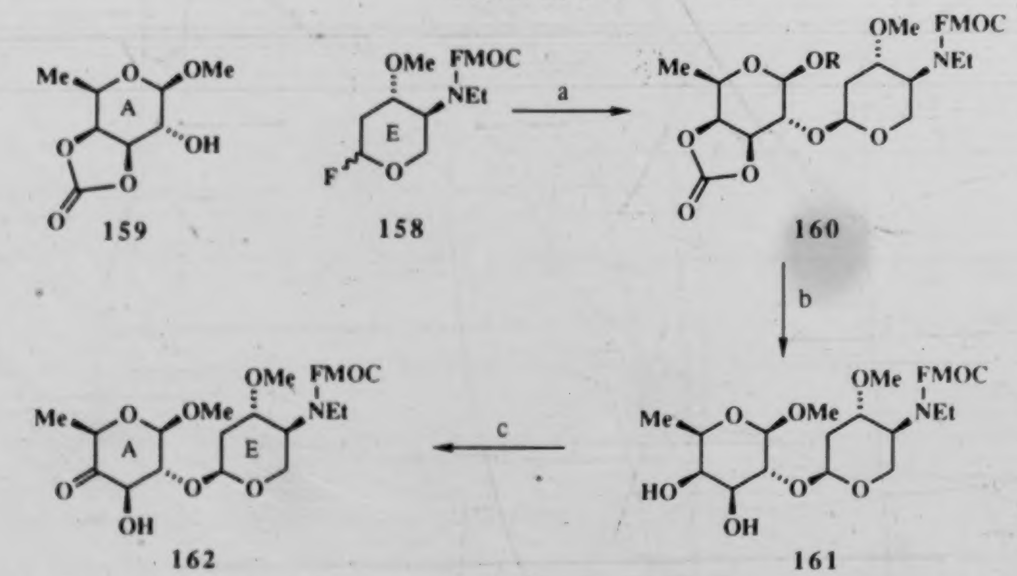
SCHEME 23


HO
RNH
CO₂Me
a
146 R = H.HCl
147 R = Et
b
O
O=
N
R
Et
c
148 R = CO₂Me
149 R = CHO
d
OR
e
150 R = OH
151 R = Me
f
X
OMe
g
152 X = O
153 X = (OMe)₂
h
HO
HN
Et
OMe
OMe
OMe
154
i
EtHN
OMe
OMe
155a and 155b
j
EtN
R
156
k
OH
157
l
F
E
158
R = FMOC =

Scheme 23. Reagents and conditions: (a) Et$_3$N, MeOH, 0 °C, 10 min, then MeCHO, 0 °C; then NaBH$_4$, 0 °C, 64%; (b) carbonyldiimidazole, MeCN, 80 °C, 66%; (c) DIBAL-H, CH$_2$Cl$_2$, -78 °C, 75%; (d) 1.3 equiv (-)-β-methoxydiisopinocampheylborane, 1.3 equiv allylmagnesium bromide, THF, -78–25 °C; then pH 7 buffer; MeOH-30% H$_2$O$_2$ (3:1), 0 °C, 1 h, 75%; (e) 1.2 equiv Ag$_2$O, 5 equiv MeI, DMF, 40 °C, 92%; (f) O$_3$, CH$_2$Cl$_2$/MeOH (1:1), -78 °C; then P(OMe)$_3$, -78–25 °C, 91%; (g) MeOH, Amberlyst-15, 25 °C, 85%; (h) NaOH, MeOH/H$_2$O (2:1), 90 °C, 96%; (i) HCl, MeOH, 88%; (j) FMOC-Cl, K$_2$CO$_3$, THF/H$_2$O (7:3), 0 °C, 96%; (k) AcOH/H$_2$O (4:1), 90 °C, 85% (l) 3 equiv DAST, THF, -78–0 °C, 91%.

Coupling (Scheme 24) of fluoride **158** (ring E) with the suitably protected ring A derivative **159** (synthesized from D-galactose) afforded dissacharide **160** in 70% yield, together with its β-anomer (16%).[38] Chromatographic separation and removal of the carbonate moiety gave the diol **161** which was selectively oxidized at C-4. This sequence furnished ketone **162** which represents a derivative of the subunit AE in a form suitable for coupling with ring B.

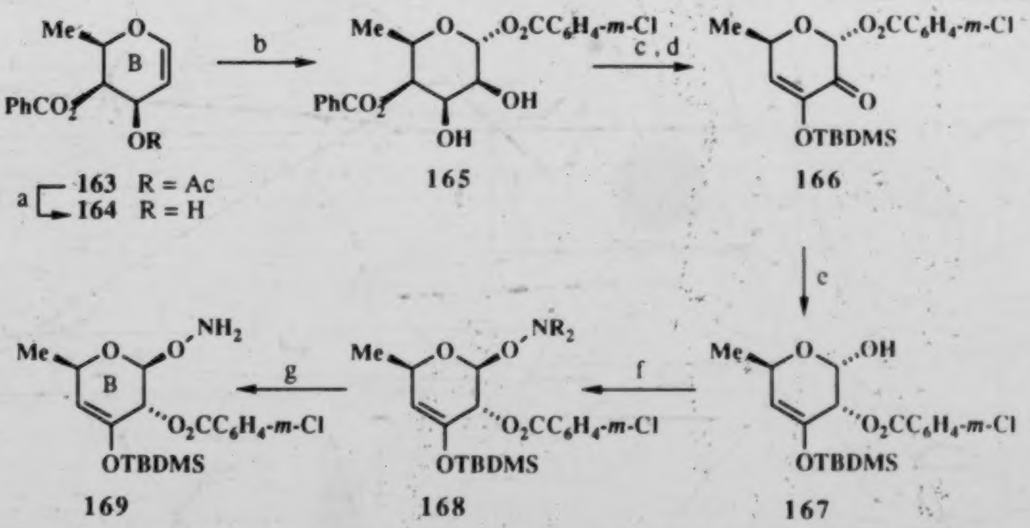
SCHEME 24


Me
OMe
A
OH
O
O
O
159
OMe
FMOC
NEt
E
F
O
158
a
Me
O
OR
OMe
FMOC
NEt
160
b
OMe
FMOC
NEt
Me
OMe
HO
OH
161
c
Me
OMe
FMOC
NEt
A
E
O
OH
162

Scheme 24. Reagents and conditions: (a) 1.2 equiv **159**, 1.5 equiv **158**, 2.0 equiv $AgClO_4$, 2.0 equiv $SnCl_2$, THF, -78 to -20 °C, 86%, (α/β ratio 4.5:1); (b) 0.01 equiv NaH, $HOCH_2CH_2OH$/THF (1:20), 93%; (c) 1.0 equiv Bu_2SnO, MeOH, 65 °C, 45 min; then 1.0 equiv Br_2, 1.0 equiv Bu_3SnOMe, CH_2Cl_2, 25 °C, 0.5 h, 70% plus 11% recovered **161**.

Ring B was synthesized from the diester **163** which, in turn, was made from D-glucose.[42] Thus, following selective deprotection of the diester **163**, epoxidation of **164** with *m*-chloroperbenzoic acid followed by regio- and stereoselective epoxide opening by *m*-chlorobenzoic acid afforded diol **165** in 55% yield (Scheme 25).

SCHEME 25


Me
O
B
PhCO₂
OR
a
163 R = Ac
164 R = H
b
Me
O
O₂CC₆H₄-m-Cl
PhCO₂
OH
OH
165
c, d
Me
O
O₂CC₆H₄-m-Cl
O
OTBDMS
166
e
Me
O
OH
O₂CC₆H₄-m-Cl
OTBDMS
167
f
Me
O
O
NR₂
O₂CC₆H₄-m-Cl
OTBDMS
168
g
Me
O
B
O
NH₂
O₂CC₆H₄-m-Cl
OTBDMS
169

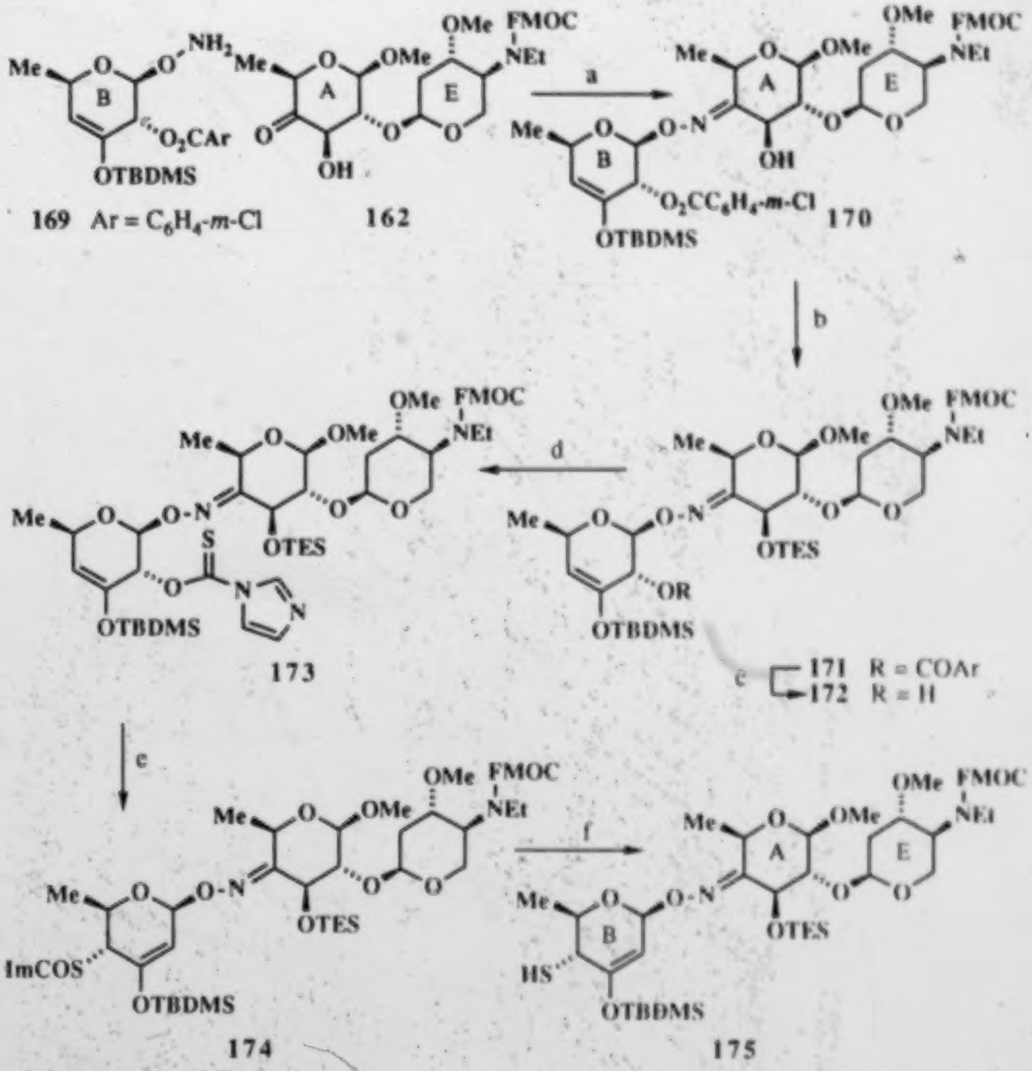
Scheme 25. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, -78 °C, 72%, plus 15% recovered **163**; (b) 55% *m*-CPBA, $MgSO_4$, CH_2Cl_2, 0 °C, 55%; (c) *t*-$BuMe_2SiCl$, imidazole, CH_2Cl_2, 67%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78–25 °C, 88%; (e) $Zn(BH_4)_2$, NH_4Cl, ether, 0 °C; (f) HO-NPhth, DIAD, Ph_3P, THF, 53% overall from **166**; (g) N_2H_4, MeOH, 92%.

Selective silylation of the 3-hydroxyl group of **165** followed by exposure to Swern conditions resulted in formation of enone **166** via an oxidation-elimination sequence. 1,2-Reduction of the enone proceeded smoothly from the β-face and was followed by the expected[43] *in situ* ester migration, to afford the desired α-lactol **167** (*ca* 8:1 α:β ratio) in good yield. Rapid workup, followed immediately by addition of *N*-hydroxyphtalimide, triphenylphosphine, and diisopropyl azodicarboxylate resulted in formation of the β-glycoside **168**. An S_N2 process is thought to be occuring here, because the α:β ratio of the resulting glycoside **168** is dependent upon the ratio of the starting lactol anomers. Liberation (hydrazine) of the amino group led to the hydroxylamine derivative **169** (ring B). Again, this compound is suitably set up for coupling with the AE subunit **162**.

Coupling of ketone **162** (ring AE) with hydroxylamine **169** (ring B) led to trisacharide **170** (ring BAE) via oxime formation (Scheme 26).[38] Silylation of **170** and exposure to DIBAL-H gave the hydroxy compound **172**. The latter was treated with thiocarbonyldiimidazole to give the key thionoimidazolide **173** . Thermolysis of **173** resulted in a [3,3]-sigmatropic rearrangement which produced thioester **174** and thereby introduced the sulfur moiety at C-4 of ring B. Exposure of the thioimidazolide **174** to sodium methylthiolate led to the rather labile thiol **175** (95% crude yield). Compound **175** represents the BAE subunit.

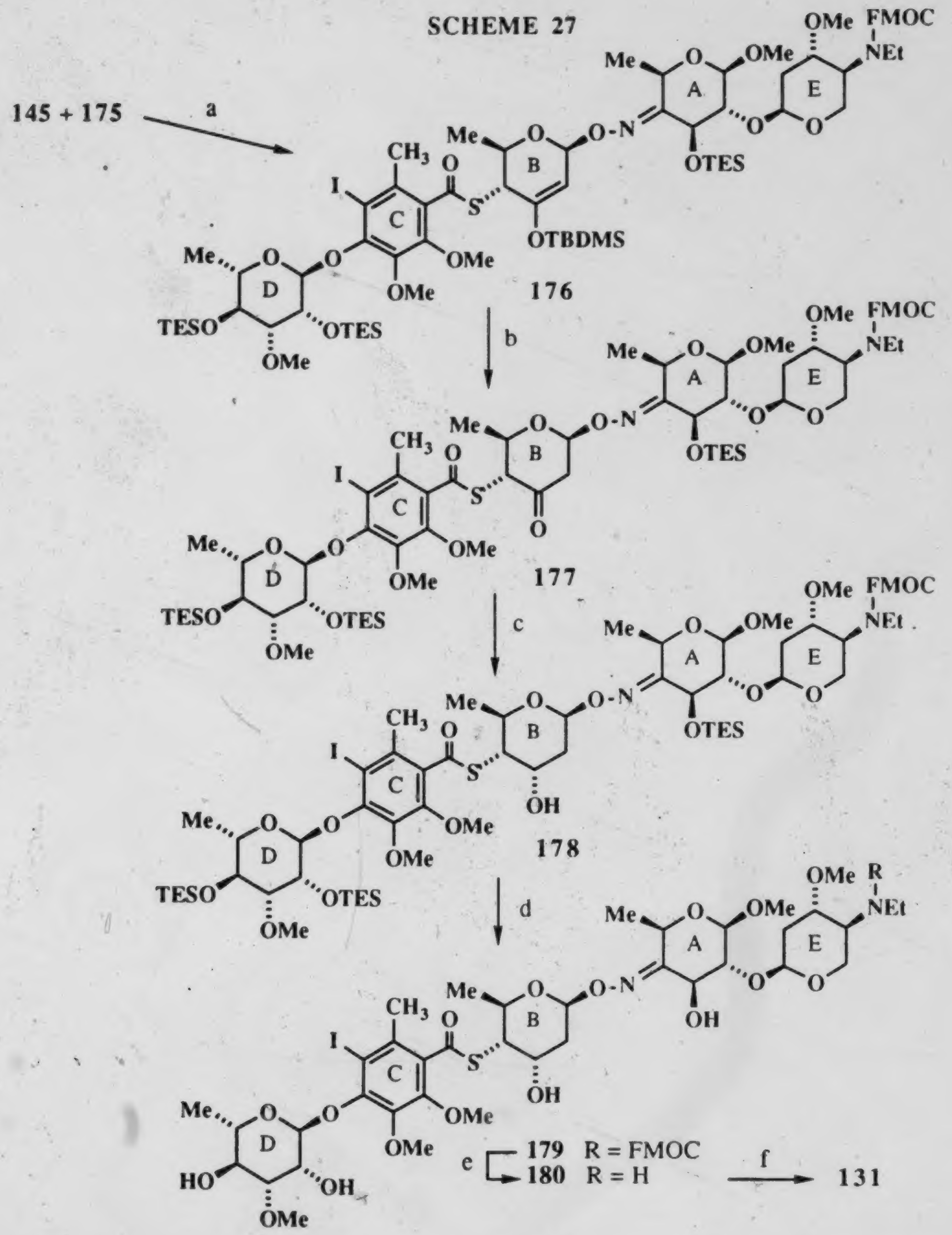
Coupling of thiol **175** (subunit BAE) and acid chloride **145** (subunit CD) afforded the CDBAE subunit **176** (Scheme 27). Monodesilylation of the enol ether moiety (1.0 equiv Bu_4NF) resulted in the ketone **177**. This was selectively reduced with K-Selectride to afford the axial α-hydroxy compound **178** in 75% overall yield from **176**. Removal of all three triethylsilyl groups from **178** and removal of the FMOC group then led to **180** in 87% overall yield. Finally, reduction of the oxime double bond in **180** with sodium cyanoborohydride in methanol furnished the target oligosaccharide **131**, together with its C-4 epimer (90% yield, *ca* 1:2 ratio). The correct (minor) isomer was isolated and compared with a closely related derivative made by degradation of calicheamicin $\gamma_1{}^I$.

SCHEME 26


169 Ar = C6H4-m-Cl
162
170
171 R = COAr
172 R = H
173
174
175
a
b
c
d
e
f
OMe
FMOC
NEt
OTBDMS
OTES
OH
ImCOS
HS
A
B
E

Scheme 26. Reagents and conditions: (a) 1.2 equiv **169**, 1.0 equiv **162**, 0.05 equiv PPTS, PhH, 83%; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0–25 °C, 100%; (c) DIBAL-H, CH_2Cl_2, -78 °C, 91%; (d) thiocarbonyldiimidazole, MeCN, 87%; (e)$PhCH_3$, 110 °C, 98%; (f) NaSMe, 50 equiv EtSH, CH_2Cl_2, 0 °C, 95%.

SCHEME 27


145 + 175
a
176
b
177
c
178
d
e
179 R = FMOC
180 R = H
f
131
A
B
C
D
E
OMe
FMOC
NEt
Me
OTES
OTBDMS
TESO
CH3
I
S
O-N
OH
HO
R

Scheme 27. Reagents and conditions: (a) 1.3 equiv **145**, 1.0 equiv **175**, 5 equiv Et_3N, DMAP cat., CH_2Cl_2, 0 °C, 80%; (b) 1.0 equiv TBAF, 4.0 equiv AcOH, THF, -23 °C,; (c) K-Selectride, DME/THF (8:1), -78 °C, 75% overall from **176**; (d) HF.pyridine, CH_2Cl_2/THF (15:1), 0 °C, 87%; (e) Et_2NH/THF (1:1), 100%; (f) $NaBH_3CN$, MeOH-HCl(g) (pH 3), 0 °C, 90%, *ca* 1:2 ratio in favor of the wrong isomer.

II. RESULTS AND DISCUSSION

From the above review it is clear that a great deal of research has been directed towards the total synthesis of calicheamicin γ_1^I. The perceived importance of the compound and its analogs, both for the purpose of understanding their biological properties and as a challenge to synthetic chemistry, will no doubt stimulate further work in this field.

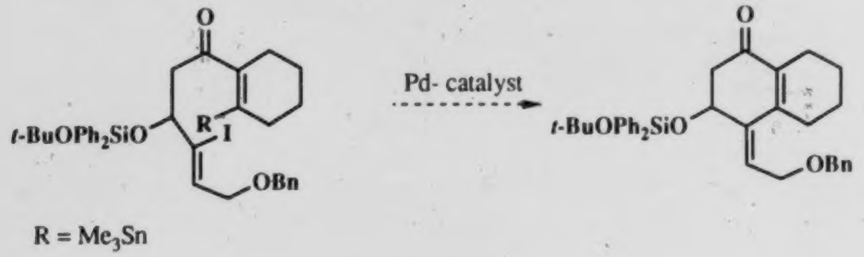
The subunit of calicheamicin γ_1^I that seemed to pose an obvious challenge from the synthetic point of view is the aglycon portion, calicheamicinone, and we decided therefore that it would be our target.

After a very brief investigation directed towards simple models of the central core, we decided to undertake the synthesis of the actual core itself. It was appreciated of course, that this would constitute a major undertaking and we recognized that the presence of the urethane functionality would be a serious complicating factor.

At the time we started the synthesis, every single report relating to calicheamicin synthesis was on models, and all lacked the urethane moiety. Only very recently was the total synthesis of calicheamicinone reported by Danishefsky *et al.*[32] and it has been made very clear that 'the elusive urethane' as they qualified it, did indeed pose a serious problem.

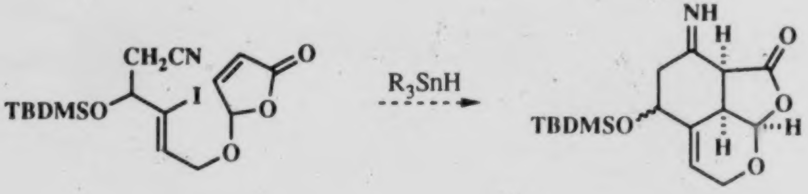
In the following paragraphs, three different preliminary studies will be discussed:

A) Model studies that probe the viability of an intramolecular palladium-mediated coupling of a vinyl iodide with a vinyl stannane for the construction of the conjugated diene of calicheamicinone (Equation 3).



Eq. 3

B) An approach based on radical cyclization that would set up an advanced skeleton related to calicheamicinone in a few steps (Equation 4).

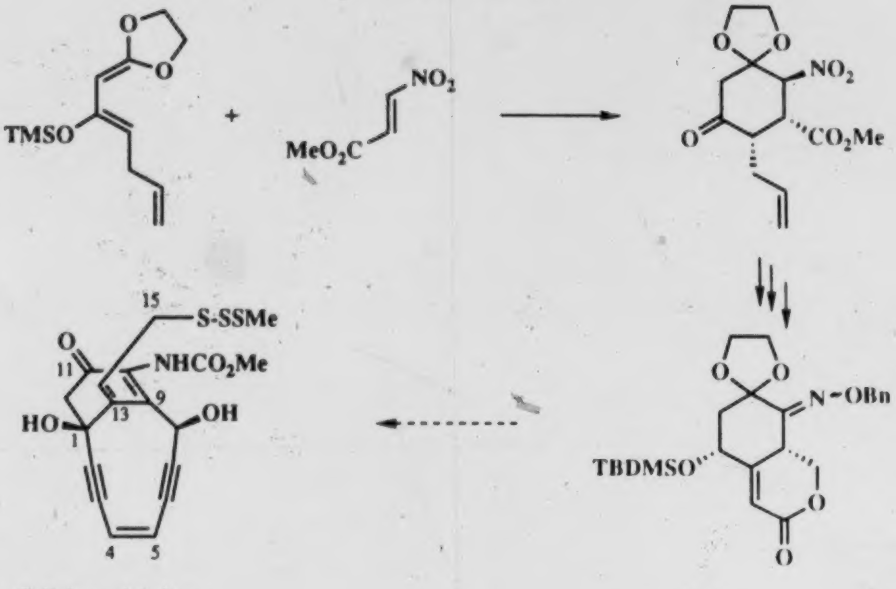


Eq. 4

C) An approach based on a Diels-Alder reaction for construction of the six-membered ring of calicheamicinone in a way that provides the nitrogen functionality at C-10 that is needed for elaboration to the target (Scheme 28).

#The numbering of the carbons is the one designated for calichaemicinone (Scheme 28). The same numbering will be used througout the discussion for compounds representing potential precursors of calicheamicinone.

SCHEME 28

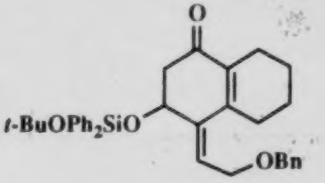

TMSO
MeO$_2$C
NO$_2$
NO$_2$
CO$_2$Me
N–OBn
TBDMSO
15
S-SSMe
NHCO$_2$Me
11
13
9
HO
OH
1
4
5

Calicheamicinone

As the first two approaches met with limited success, we will present the results together with some general outlines only. The third approach looks, at the present time, much more promising and it will be discussed in greater detail.

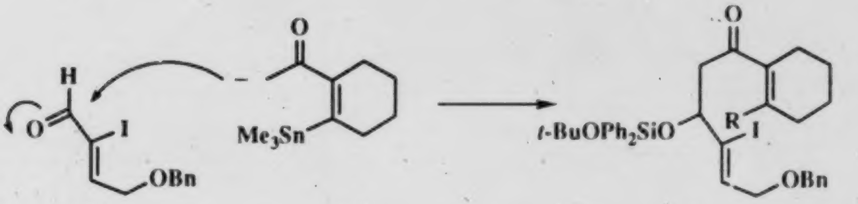
A) PALLADIUM COUPLING APPROACH

Our first approach was to evaluate a palladium-mediated coupling that would lead to the conjugated diene portion of calicheamicinone. The target molecule of this sequence was **181**.



181

According to our plan, **181** would be constructed by aldol condensation of iodo aldehyde **182** with stannyl enolate **183**, to give **184**, followed by intramolecular palladium-catalyzed coupling of the two moieties (Equation 5).

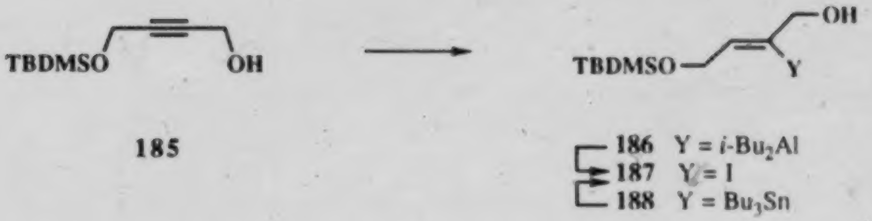


182 **183** **184** R = Me$_3$Sn

Eq. 5

The first routes envisioned for preparation of the iodo aldehyde **182** involved either directed hydroalumination[44] of the mono protected diol **185** followed by treatment with iodine (Scheme 29) to give **187**, or treatment with tributyltin hydride/AIBN to give **188**, and then with iodine[45] to give **187**. Both methods proved to be unsatisfactory and a better route was devised. This route will be discussed later (Scheme 32).

SCHEME 29

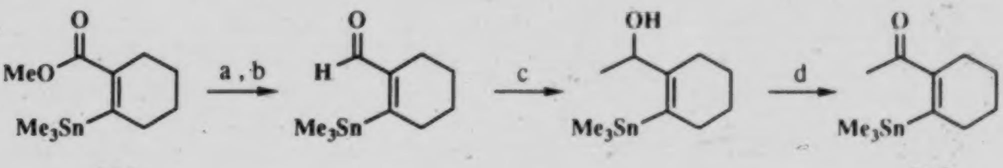


185

186 Y = i-Bu_2Al
187 Y = I
188 Y = Bu_3Sn

The stannyl ketone **190** (*cf.* **183**) was easily made in four steps from the known ester **189**,[46] as shown in Scheme 30.

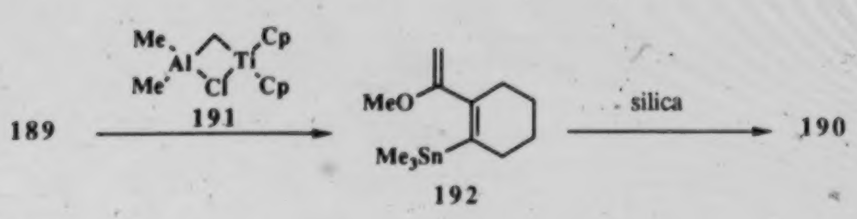
SCHEME 30



189 **190**

Scheme 30. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, -78 °C, 87%; (b) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, 15 min followed by Et_3N, -78 °C, 30 min, 66%; (c) MeMgBr, Et_2O, -20 °C, 95%; (d) as in (b), 65%.

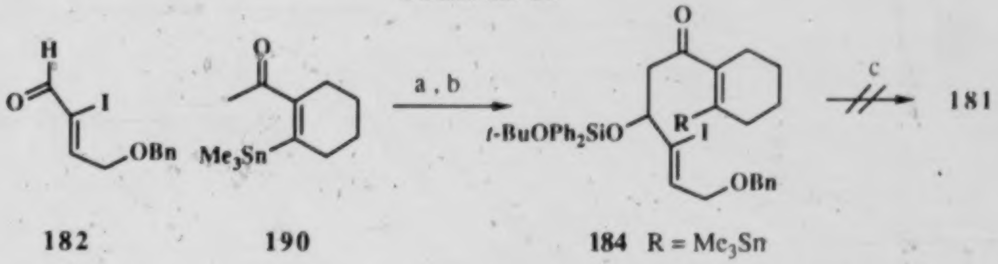
Alternatively, treatment of ester **189** with Tebbe's reagent **191** (Equation 6) gave enol ether **192** which, after flash chromatography on silica, gave the desired ketone **190** directly (26%) along with large amounts of recovered starting material. Although the yield is rather low, we believe that the yield can be raised to a much higher value by using better quality reagent; however this opinion was not tested.


189
Me
Me
Al
Cl
Ti
Cp
Cp
191
MeO
Me$_3$Sn
192
silica
190

Eq. 6

Aldol condensation of ketone **190** with aldehyde **182** proceeded well, providing that the deprotonation step was not done at too low a temperature (-35 °C) (Scheme 31). The crude aldol product was converted into the silyl ether **184** (57% overall). Attempted palladium-mediated coupling resulted in total decomposition (baseline material on TLC). Brief attempts to homolyze the carbon-iodine bond, so as to form a radical that could undergo 6-endo closure were also unsuccessful. Likewise, treatment of **184** with butyllithium, in the hope of generating a carbanion by halogen-lithium exchange, were unpromising, and so the general approach of Scheme 31 was abandoned.

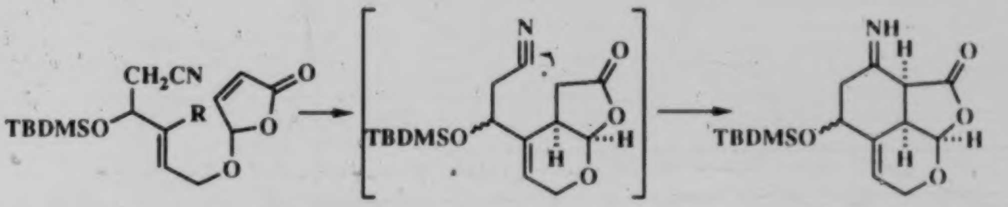
SCHEME 31


H
O
I
OBn
O
Me$_3$Sn
a , b
O
t-BuOPh$_2$SiO
R
I
OBn
c
181
182
190
184 R = Me$_3$Sn

Scheme 31. Reagents and conditions: (a) LDA, Et$_2$O, -35 °C, 40 min, cool to -78 °C; add **182**, 15 min; (b) *t*-BuOPh$_2$SiCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 57% overall; (c) (Ph$_3$P)$_4$Pd, CH$_3$CN; or PdCl$_2$(CH$_3$CN)$_2$, CH$_3$CN; or Bu$_3$SnH, AIBN, PhH, reflux; or BuLi, THF, -78 °C.

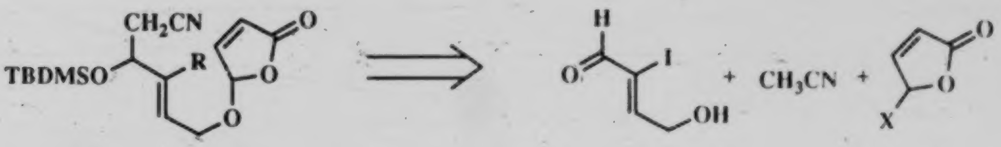
(B) RADICAL CYCLIZATION APPROACH

The second strategy was based on an intramolecular radical cyclization. It was thought that treatment of compound **193** with tributyltin hydride and AIBN under standard conditions would generate the vinyl radical **194** (Equation 7). This could undergo two consecutive 6-exo trig radical closures so as to lead to **195** which represents a relatively advanced precursor of calicheamicinone.


CH₂CN
TBDMSO
R
O
O
O
N
O
O
TBDMSO
H
H
O
NH
H
O
O
TBDMSO
H
H
O

193 R = I
194 R = .
195
Eq. 7

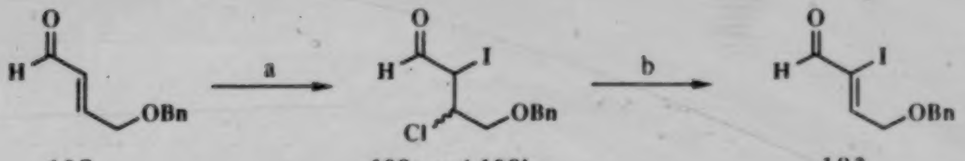
Judicious bond disconnection in **193** suggests three synthons, a valerolactone unit, acetonitrile, and a vinyl iodide **196** that is accessible from the previously discussed iodoaldehyde **182** The preparation of the iodide **182** was achieved as follows:


CH₂CN
TBDMSO
R
O
O
O
H
O
I
OH
+ CH₃CN +
O
O
X

193
196

Treatment of the known aldehyde **197**[47] with mercuric chloride and iodine gave a mixture of two isomeric chloroiodides [^{1}H NMR (90 MHz)] **198a** and **198b** in 96% yield (Scheme 32).

SCHEME 32



197 **198a** and **198b** **182**

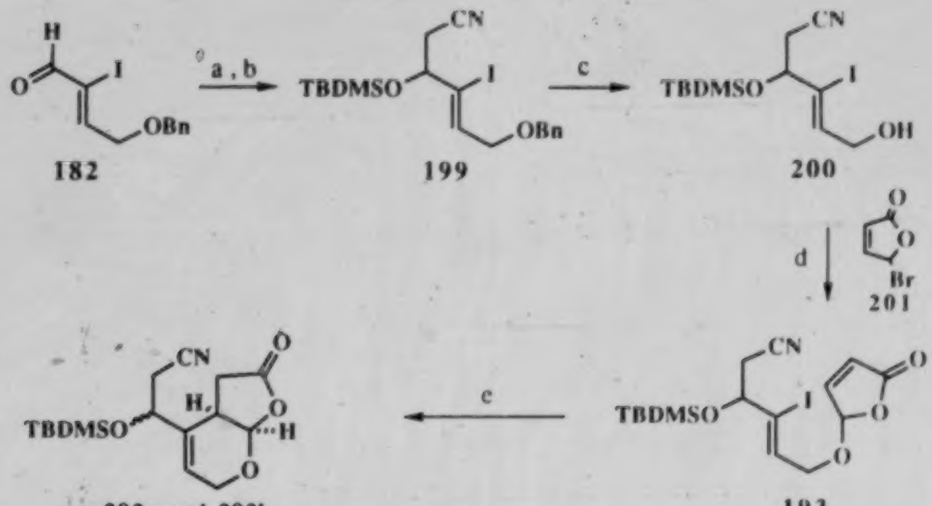
Scheme 32. Reagents and conditions: (a) $HgCl_2$, I_2, CH_2Cl_2; (b) AcOK, AcOH, 71% overall.

At the time this experiment was done we were not aware of any report using mercuric chloride/iodine as a source of ICl, but we eventually found that it had been used with simple, symmetrical, and non functionalised alkenes.[48]

Treatment of the mixture of chloroiodides **198a** and **198b** with potassium acetate in acetic acid provided the desired iodoaldehyde as a single isomer in 82% yield. The success of this transformation is based on the fact that unsaturated aldehydes have a very high propensity to isomerize to the *trans* geometry. Therefore the *cis* aldehyde produced from one of the two chloroiodides isomerizes under the reaction conditions, and only the *trans* compound **182** is isolated. [Very few reports of iodo alkenals are found in literature and we first suspected that this was due to their instability. We found however that **182** could be stored in the freezer (-15 °C) for several weeks without significant decomposition.]

Deprotonation of acetonitrile followed by quenching of the resulting enolate with aldehyde **182** gave the aldol adduct (Scheme 33), and this was silylated to **199** (70% overall). Removal of the benzyl protecting group was achieved with boron tribromide so as to afford alcohol **200** (90%). It will be noted that cleavage does not take place to any detectable extent at the allylic position but only at the benzylic position (which, of course, is also allylic). The factors responsible for this regioselectivity are not known. Coupling of **200** with 5-bromo-2(5*H*)-furanone[49] **201** gave the required cyclization precursor **193** in 50% yield as a mixture of two isomers (^{13}C NMR).

SCHEME 33

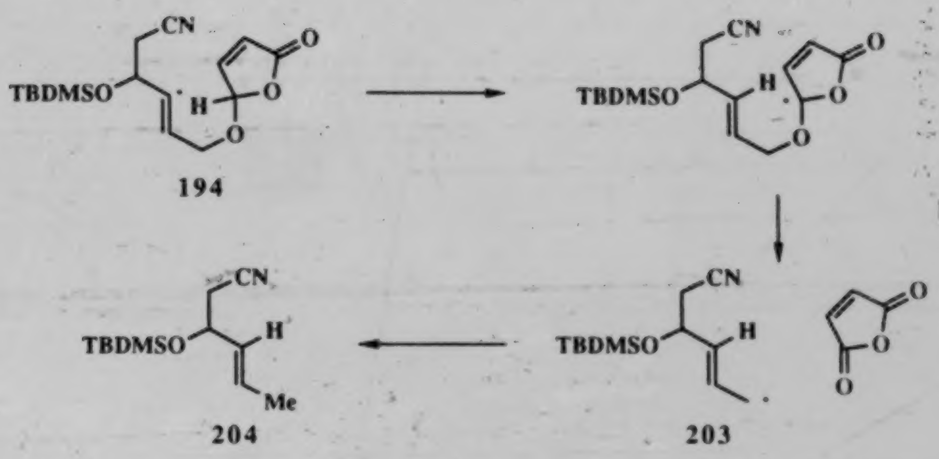

H
O
I
OBn
182
a, b
CN
TBDMSO
I
OBn
199
c
CN
TBDMSO
I
OH
200
d
O
O
Br
201
CN
TBDMSO
I
O
O
O
193
e
CN
O
H
O
H
TBDMSO
O
202a and 202b

Scheme 33. Reagents and conditions: (a) CH_3CN, LDA, Et_2O, -78 °C, 30 min; add **182** slowly, 1 h, 71%; (b) TBDMSCl, imidazole, DMF, 35 °C, 16 h, 99%; (c) BBr_3, CH_2Cl_2, 0 °C, 92%; (d) AgOTf, 2,4,6-collidine, 5-bromo-2(5*H*)-furanone **201**, CH_3NO_2, 50%; (e) Bu_3SnH, AIBN, PhH, reflux, **202a**:**202b**::1:1 ratio, 30–40%.

Treatment of **193** with tributyltin hydride/AIBN under standard conditions afforded a 1:1 mixture [^{1}H NMR (200 MHz)] of **202a** and **202b** in 30-40% yield (four experiments, 25 mg scale). Examination of the reaction mixture by TLC showed that the process was clean and revealed two spots running very close together. The ^{1}H NMR spectrum of the two compounds indicated disapearance of the vinylic hydrogens in the lactone ring of the starting material. The vinylic hydrogen of each of the two isomers resonated at δ 5.99 (t, J = 3.0 Hz) and δ 6.12 (t, J = 2.4 Hz), respectively, the signal areas being in a ratio of 1:1. The high resolution mass spectrum showed peaks corresponding to $[M - Me]^+$, $[M - C_4H_9]^+$ and $[M - CH_2CN]^+$. The FT-IR spectrum contained a weak absorption at 2260 cm^{-1}, corresponding to the nitrile, and a strong absorption at 1800 cm^{-1}, characteristic of a δ-lactone.

Attempts to improve the yield by using different conditions (triethylborane, tributyltin hydride, room temperature; triphenyltin hydride, AIBN, 80 °C;tributyltin hydride, AIBN, 110 °C) all proved unsuccessful. The reason for the low yield (even though TLC monitoring suggested that the reaction was clean) was discovered when the crude mixture from one of the experiments was analyzed by ^{1}H NMR.

A side product, in a molar ratio of *ca* 1:1 with the cyclized products, was detected. This side product is totally invisible by TLC but was nevertheless isolated and identified as structure **204** (in which the Z geometry is an arbitrary assignment) (Equation 8). The compound arises quite probably by abstraction of the hydrogen present on the acetal moiety by the vinyl radical, followed by C-O cleavage to produce an allylic radical **203**. This leads to **204** after hydrogen abstraction from stannane.



Eq. 8

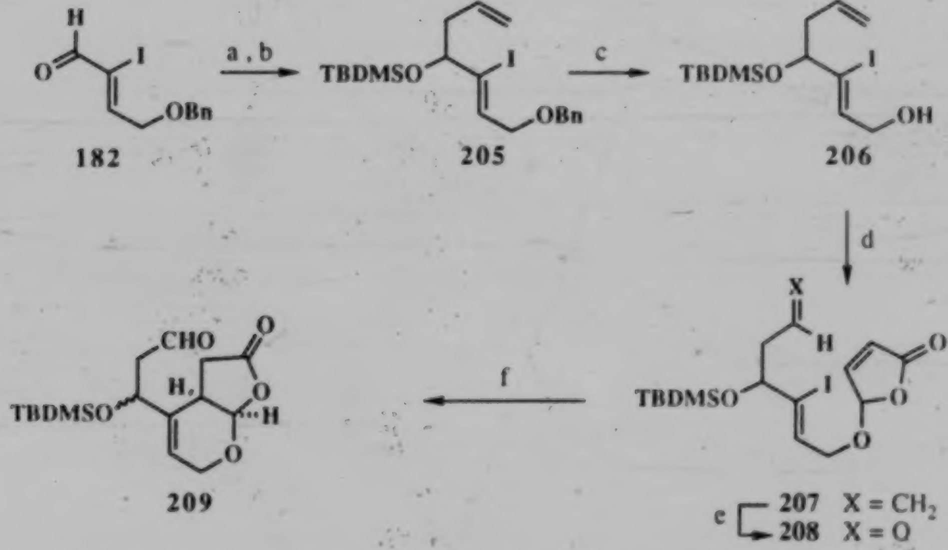
Attempts to do the cyclization using the corresponding aldehyde **208** were also conducted (Scheme 34). The rational behind this decision was that aldehydes have been shown to be excellent radical acceptors,[50] and this property would favor the second cyclization. Using the same conditions as for **193**, a compound tentatively assigned structure **209**, on the basis of its ^{1}H NMR spectrum was obtained in 31% yield. The synthesis of the aldehyde precursor **208** is shown in Scheme 34. The yields were not optimized.

The fact that only a single cyclization would take place with both nitrile and aldehyde was not a serious problem because, in principle, the second cyclization could be performed using ionic chemistry (aldol).

However, the yield of this single cyclization would have to be improved, and it was decided to perform the cyclization with esters **212** to **214** as opposed to acetals **193** or **208**. The possibility of hydrogen abstraction would then be avoided.

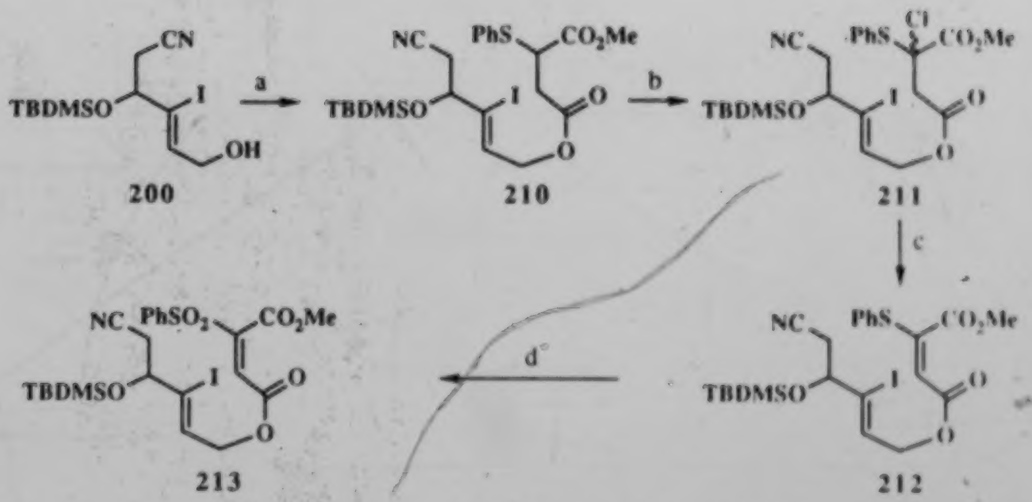
The preparation of cyclization precursors **212** to **214** is shown in Scheme 35 where the structures are tentatively assigned on the basis of ^{1}H and/or ^{13}C NMR spectra.

SCHEME 34


H
O
I
OBn
182
a, b
TBDMSO
I
OBn
205
c
TBDMSO
I
OH
206
d
X
H
TBDMSO
I
O
O
O
e
207 X = CH$_2$
208 X = O
f
CHO
O
H
O
H
TBDMSO
O
209

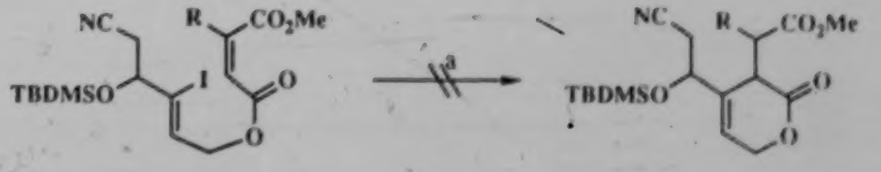
Scheme 34. Reagents and conditions: (a) CH_2CHCH_2MgBr, Et_2O, -78 to -40 °C, 30 min, 69%; (b) TBDMSCl, imidazole, DMF, 55 °C, 6 h, 93%; (c) BBr_3, CH_2Cl_2, 0 °C followed by Ag_2O, acetone-water, 39% overall; (d) 5-bromo-2(5*H*)-furanone **201**, Ag_2CO_3, 4 Å molecular sieves, $CHCl_3$, 61%; (e) OsO_4, NMMO, acetone-water; then $NaIO_4$, MeOH, 50% overall; (f) Bu_3SnH, AIBN, PhH, reflux, 31%.

SCHEME 35



Scheme 35. Reagents and conditions: (a) DEAD, Ph_3P, 2-(Phenylthio)-butanedioic 1-methyl ester, 78 °C; (b) NCS, THF-CCl_4; (c) DBU, CH_2Cl_2, 70% overall; (d) m-CPBA, CH_2Cl_2, 80%.

Treatment of **212** to **214** (Equation 9) with tributyltin hydride/AIBN under standard conditions gave invariably an intractable mixture for reasons that are not clear, although we feel that restricted rotation around the CO-O bond, which prevents the molecule from adopting the correct conformation for the cyclization to take place, is probably responsible, in part, for this negative result.



Eq. 9

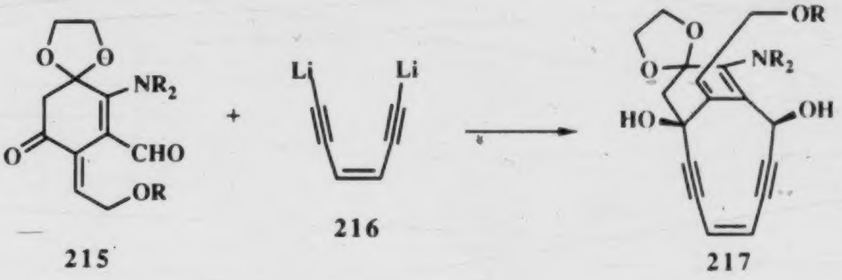
212 R = PhS
213 R = $PhSO_2$
214 R = H

Reagents and conditions: (a) Bu_3SnH, AIBN, PhH, reflux.

Prompted by these discouraging results,[#] the radical cyclization approach was put aside, at least for the time being, while another strategy was evaluated.

(C) DIELS-ALDER APPROACH

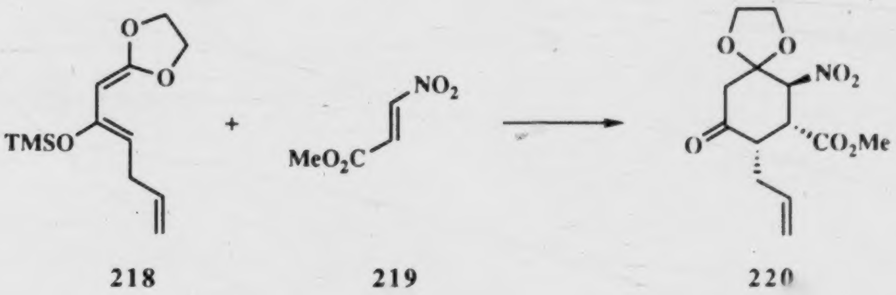
The target molecule being sought is a six-membered ring, such as **215**, that is suitably functionalised to accept a dilithioenediyne moiety **216** and form, thereby, the framework **217** of calicheamicinone (Equation 10).



O
O
NR$_2$
O
CHO
OR
+
Li
Li
OR
O
O
NR$_2$
HO
OH
215
216
217

Eq. 10

Retrosynthetic analysis of the six-membered ring **215** leads to **220** which, in turn, leads to two synthons that could be joined by Diels-Alder reaction. These synthons are diene **218** and dienophile **219** (Equation 11).



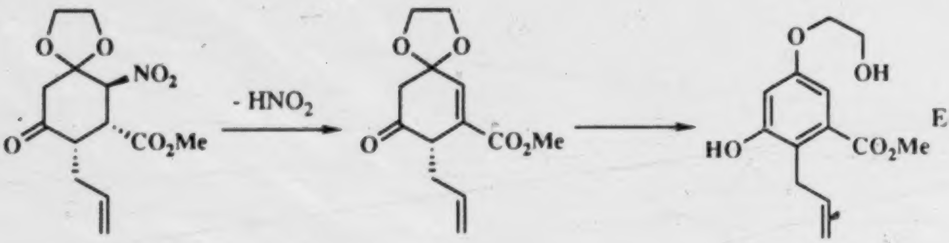
O
O
TMSO
+
NO$_2$
MeO$_2$C
O
O
NO$_2$
O
CO$_2$Me
218
219
220

Eq. 11

[##] For a review on successful and unsuccessful lactonizations by radical chemistry, see reference 51.

The features that make dienophile **219** a potentially good candidate are:

1) It would be a reactive dienophile and so allow the Diels-Alder cycloaddition to occur at a low temperature. One can imagine a process whereby **220** could aromatize to **221** (Equation 12) and such a possibility would be minimized at low temperature. A survey of the literature showed that indeed, **219** had been used[52] in Diels-Alder reactions and proved to be quite reactive.



Eq. 12

220 **221**

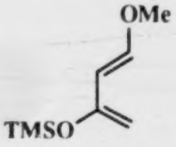
2) Compound **219** must react in the desired regiochemical sense. The nitro group being potentially an excellent director suggested that the nitrogen group might end up α to the ketal, and we later found a report[52a] in the literature that this was indeed the way that **219** would behave.

3) Reaction of **218** with dienophile **219** would produce **220**, which possesses the nitrogen functionality (NO_2) required for future elaboration into the urethane moiety of calicheamicinone. Moreover a carbonyl moiety (CO_2Me) is present and this should be easily converted into the corresponding aldehyde.

The important features of the diene **218** are:

1) Reaction of diene **218** with dienophile **219** would provide **220** with the two ketone functionalities necessary for elaboration into calicheamicinone but, more importantly, with one ketone differentiated from the other as an ethylene ketal.

2) The fact that diene **218** has similar features to those present in Danishefsky's diene **222** (a well known reactive diene) implies that it will be at least as reactive and possibly more so because two oxygens atoms (ethylene ketal) are present as compared to only one (OMe) in **222**. Moreover, the two oxygens atoms are locked in a conformation where two of their electron-pairs orbitals, are perfectly aligned with the π orbitals of the diene moiety, for full conjugation with the latter. The net result is a more efficient activation of the diene.



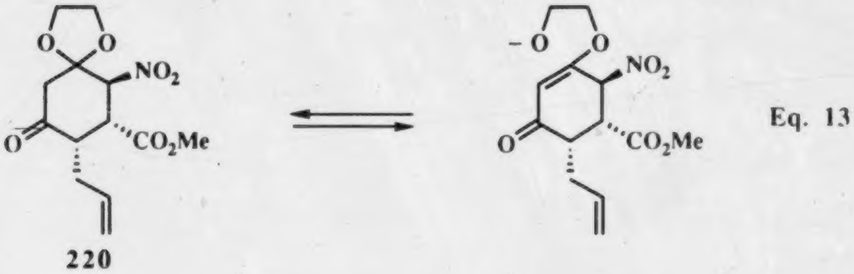
222

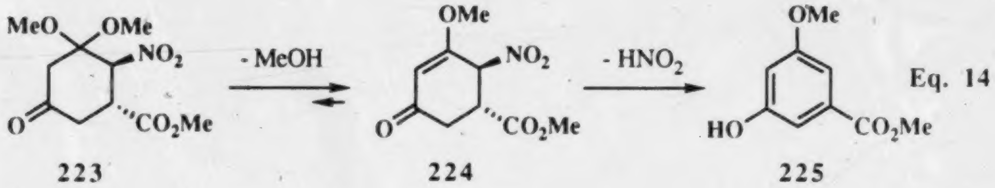
3) The tail present in diene **218** would provide, after ozonolysis of the terminal double bond to generate an aldehyde, the two carbon unit present in calicheamicinone, with the terminal carbon bearing an oxygen functionality.

4) The tail will not make the diene particularly high-boiling. This is an important attribute if one considers that, quite likely, the only way of

purifying the potentially very moisture sensitive ketene acetal derivative **218** will be by distillation.

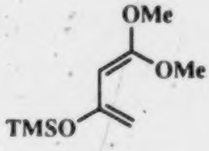
5) The presence of the ethylene ketal, as opposed to a dimethoxy ketal could play a major role in preventing aromatization of the core **220**. Indeed, if, under the conditions used for preparing **220**, bases or acids are present (which will be the case), elimination of one oxygen of the ethylene ketal could take place. However this process would be reversible (Equation 13). In contrast, if the same reaction occurs with the dimethoxy derivative **223**, reversibility is negligible and the intermediate **224** will be likely to aromatize easily (Equation 14).


O
O
NO₂
O
CO₂Me
220
– O
O
NO₂
O
CO₂Me
Eq. 13


MeO
OMe
NO₂
O
CO₂Me
223
- MeOH
OMe
NO₂
O
CO₂Me
224
- HNO₂
OMe
HO
CO₂Me
225
Eq. 14

While the synthesis of diene **218** was being developed, some preliminary studies were undertaken on models in order to evaluate the ease of aromatization of compounds of similar type to **220**.

Diene **226** is easily accessible[52b] and was used in these model studies. Treatment of **226** with methyl nitroacrylate at room temperature, followed by treatment, *in situ*, with TBAF afforded the benzene derivative **225**. Aromatization had indeed taken place easily.

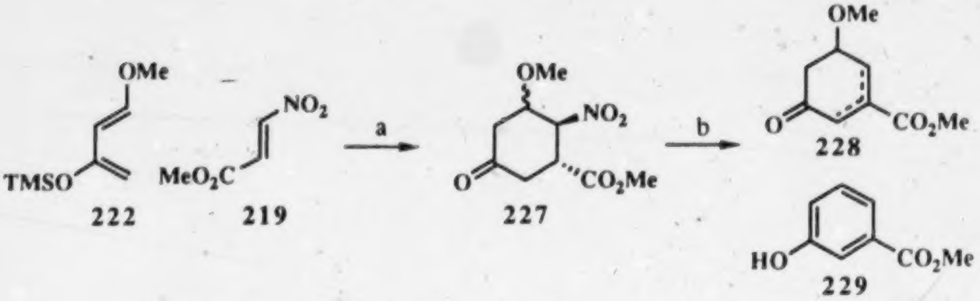


226

We then came across a report by Danishefsky *et al*[52a] which proved to be an invaluable source of information. The reactivity of dienophile **219** with certain dienes (including Danishefsky's Diene **222**) had been tested (Scheme 36). As expected, the ease of aromatization of the cycloadduct **227** was not negligible, but interestingly, the latter could be isolated providing that carefully chosen conditions were used. A potential minor problem was apparent, however. The cycloaddition gave rise to a mixture of two compounds **227**, epimeric at C-11#, that arose from a transition state where the CO_2Me group of the dienophile **219** had no endo/exo preference and if this happened in our case (i.e. with diene **218**), it would be necessary to carry out the subsequent transformations on a mixture of isomers.

#The numbering of the carbons is the one designated for calichaemicinone (Scheme 28). The same numbering will be used througout the discussion for compounds representing potential precursors of calicheamicinone.

SCHEME 36

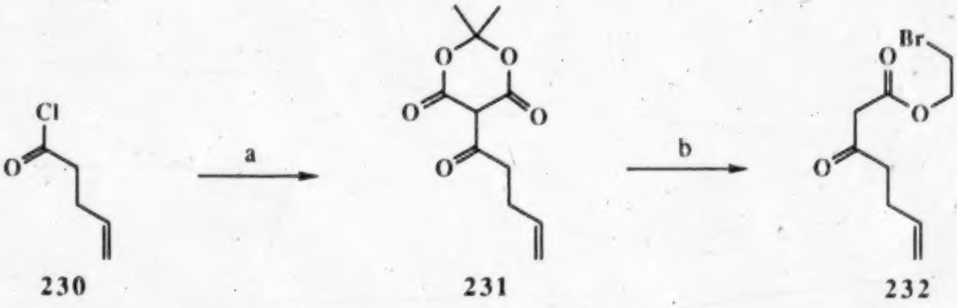

OMe
TMSO
222
NO$_2$
MeO$_2$C
219
a
OMe
NO$_2$
O
CO$_2$Me
227
b
OMe
O
CO$_2$Me
228
HO
CO$_2$Me
229

Scheme 36. Reagents and conditions: (a) Neat, 1 h; then HCl (0.005 M) in THF-water, 82%; (b) DBU, THF.

Notwithstanding the danger of aromatization, we felt that an approach to the core of calicheamicinone based on a Diels-Alder reaction should be attempted, and so we carried out the synthesis of diene **218**.

The first route involved preparation of bromide **232** by treatment of 5-pentenoyl chloride **230** with Meldrum's acid, followed by conversion of the crude adduct **231** to bromide **232** using 2-bromoethanol (Scheme 37). However, for multigram scale synthesis, the corresponding chloro derivative **234** turned out to be more convenient to prepare and we now prefer the route described below.

SCHEME 37

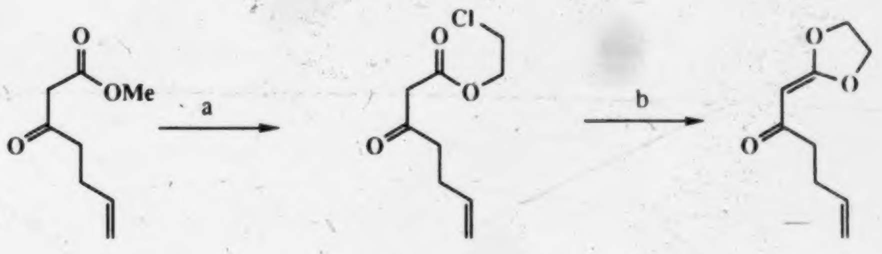

Cl
O
230
a
O
O
O
O
O
231
b
Br
O
O
O
232

Scheme 37. Reagents and conditions: (a) Meldrum's acid (0.9 equiv), pyridine (2 equiv), CH_2Cl_2; (b) 2-bromoethanol (3 equiv), PhH, reflux, 55% overall.

The readily accessible methyl β-keto ester **233**[54] was converted to **234** in good yield (*ca* 66%) by treatment[55] with 2-chloroethanol in the presence of titanium tetraisopropoxide (Scheme 38). Surprisingly, conversion of **234** into ketene acetal **235** using sodium hydride in THF failed (unlike in the case of bromide **232** where **235** was obtained in 85% yield), but the ketene acetal was eventually prepared (87%) using potassium carbonate in DMF.[55]

Preparation of diene **218** from **235** proved to be troublesome, but was achieved after some effort. The difficulties encountered are, in my opinion, due to two main factors:

SCHEME 38

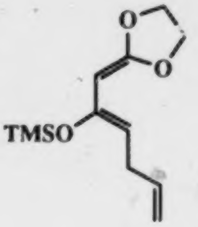


233 **234** **235**

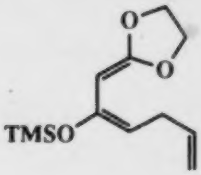
Scheme 38. Reagents and conditions: (a) Ti(i-OPr)$_4$, 2-chloroethanol, 75 °C, *ca*. 66%; (b) K_2CO_3, DMF, 87%.

1) Compound **218** possesses a ketene acetal moiety conjugated to a carbonyl and, therefore, it is very susceptible to attack by nucleophiles, including enolates. Hence conditions had to be found where no enolate would be formed in the presence of intact **235**. This can be achieved easily by slow addition of a solution of **235** to a cold solution of base at a low

temperature (kinetic conditions). However, there is a second complicating factor.



218



236

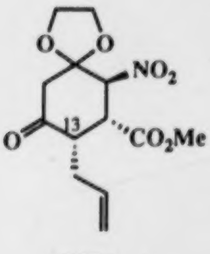
2) The allyl group linked to the diene should preferably be *syn* to the silyloxy group, since dienes with (*E*) geometry are known to be rather unreactive in Diels-Alder reactions. The use of normal kinetic conditions (lithium diispropylamide, -78 °C) gives a (7:3) mixture in favor of the wrong isomer **236**.

A solution to the problem was found when the reaction was done under kinetic conditions using a different base. When lithium hexamethyldisilazide was used at -78 °C, the desired **218** was the major compound and predominated over the other isomer by a factor of 3 to 2. This result showed that the nature of the base could drastically influence the ratio of isomeric enolates, and indeed, this had been confirmed by a report by Masamune[56] in which 3-pentanone was deprotonated under kinetic conditions using a wide variety of bases. Many bases afforded different ratios of isomeric enolates. Interestingly, lithium hexaethyldisilazide [$(Et_3Si)_2NLi$] and $(Me_2PhSi)_2NLi$ gave the desired (Z) enolate almost exclusively .

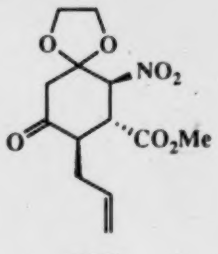
In our case, treatment of **235** with lithium bis(dimethylphenyl)silazide [$(Me_2PhSi)_2NLi$] under kinetic conditions, quenching with chlorotrimethylsilane, followed by non-aqueous workup and Kugelrohr distillation gave a solution of the desired diene **218** (*ca* 100%) in $(Me_2PhSi)_2NH$. The ^{1}H-NMR spectrum showed a new signal, corresponding to the vinylic hydrogen of the enol ether, which resonated at δ 4.76 (t, J = 7.2 Hz). The methylene hydrogens resonated at δ 2.8--2.92 (m). Although determination of enol ether geometry can be done by ^{1}H NMR and ^{13}C NMR measurements,[57] this was not attempted, and we assumed that the enol ether obtained by using lithium bis(dimethylphenyl)silazide [$(Me_2PhSi)_2NLi$] had the (Z) geometry as in the case of 3-pentanone. This assumption was confirmed by determination of the stereochemistry of the allyl substituent of the Diels-Alder adduct (see following experiment).

Attempts to obtain neat diene by careful distillation failed and, therefore, it was decided to use diene **218** in the next step, as a solution in bis(dimethylphenyl)silylamine [$(Me_2PhSi)_2NH$], in the hope that the amine would not interfere with the reaction.

We now had the material in hand for the Diels-Alder cycloaddition with methyl nitroacrylate **219**. Preliminary attempts were disappointingly unsuccessful, but it was soon realized that diene **218** was not stable enough to be kept at -15 °C overnight before use. When the reaction was repeated using 1.5 equiv of freshly-prepared (*ca.* 1 hour old) diene at 0–25°C followed by brief treatment with dilute hydrochloric acid (0.005M), TLC examination of the reaction mixture after workup showed several (5) spots including a very faint one. All the compounds were isolated. Four represented byproducts coming from the diene itself and, gratifyingly, the faint spot was the desired compound **237a**. It was obtained as a white solid in 81% yield![#]



237a



237b

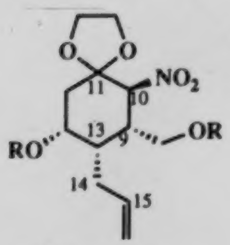
In the event, not only had the Diels-Alder reaction worked in the presence of the amine, but the product **237a** was stable enough under these conditions to be isolated. Analysis of the ^{1}H NMR spectrum showed the presence of an isomeric side product (*ca*. 11-17 mol%) but carefull crystallization afforded the pure major isomer, the mother liquor being enriched in the minor isomer. In the major isomer **237a**, the $C\underline{H}CO_2Me$ resonated at δ 3.83 (dd, J = 10.0, 5.0 Hz) and showed a large (axial-axial) coupling with $C\underline{H}NO_2$ as well as a small (equatorial-axial) coupling with $C\underline{H}$-allyl. In the minor isomer **237b**, $C\underline{H}CO_2Me$ resonated at δ 3.55 (dd, J = 10.4, 9.6 Hz) and showed a large (axial-axial) couplings with both $C\underline{H}NO_2$ and $C\underline{H}$-allyl. It will be noted that both **237a** and **237b** derive from reaction of our diene **218** with methyl nitroacrylate **219** where the CO_2Me group was *endo* to the diene moiety in the transition state of the Diels-Alder reaction.

[#] For an example of a dithioketene analog of our diene **218**, see reference 53. The reported compound met with very limited success as a diene in Diels-Alder reactions.

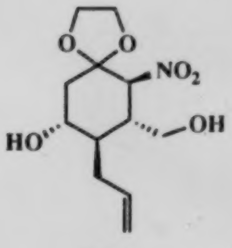
In contrast, the reaction of Danishefsky's diene **222** (page 184)with the same dienophile, as mentioned previously, gave products that arose from a transition state where the CO_2Me group had no *endo/exo* preference and therefore an epimeric mixture had ensued. In other words, in our case, the NO_2 group, controlled the regiochemistry of the cycloaddition but was exclusively *exo* to the diene moiety in the transition state leading to the cycloadduct. Electronic repulsion between the electron rich acetal of the diene and with the nitro group and/or steric hindrance offered by the ketal moiety is presumably responsible for the high stereoselectivity of the process. The formation of two isomers (**237a** and **237b**) is due to some isomerization once the ketone has formed.

We at last had a route that provided a relatively advanced precursor of the central core of calicheamicinone, and from now on all future efforts were concentrated on this approach.

We decided, at this point, to reduce both carbonyl functionalites (ketone and ester) to the corresponding hydroxyls in order to prevent the possibility of aromatization. After considerable experimentation it was found that **237a** and **237b** (83:17) could be converted into **238a** (53%) and **238b** (28%) using diisobutylaluminium hydride under carefully adjusted conditions (see experimental).



238a R = H
239 R = TBDMS



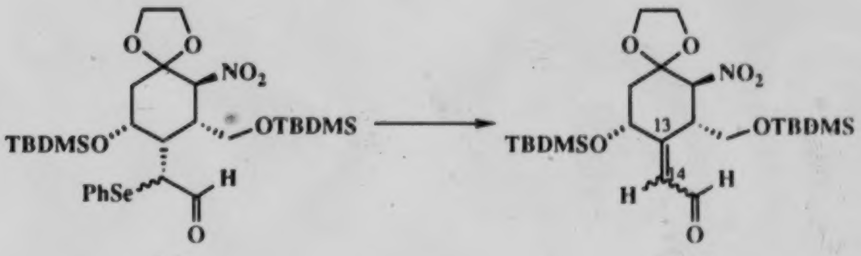
238b

It is believed that complications originated from elimination of the nitro group, (an unsaturated aldehyde was isolated on one occasion), and also by simple removal of the proton α to the nitro group (the reaction was incomplete when a stoichiometric amount of diisobutylaluminium hydride was used). It will be noted that it is most surprising to observe epimerization at C-13 under aprotic reduction conditions but unusual behavior of the present series of nitro compounds will manifest itself again in many subsequent steps.

Although, in principle, both isomers could be utilized, only the major diol **238a** was used and it was converted to the corresponding silyl ether 239 (91%). The stereochemistry of diol **238a** and its silyl ether **239** were unambiguously assigned at a later stage.

1) Studies aimed at introducing the C-13--C-15 portion stereospecifically

Our next task was to investigate how the tail (C-13 to C-15) could be obtained, and therefore our goal was selenide **240** (equation 15). Oxidation of the latter followed by selenoxide elimination would produce an α,β-unsaturated aldehyde **241** which contains the required unsaturation at C-13 and C-14. The geometry of the double bond has to correspond to the one in calicheamicinone and, since it would be formed by a selenoxide elimination (*syn* elimination), the stereochemistry of the selenide **240** would control the outcome.



240 **241**

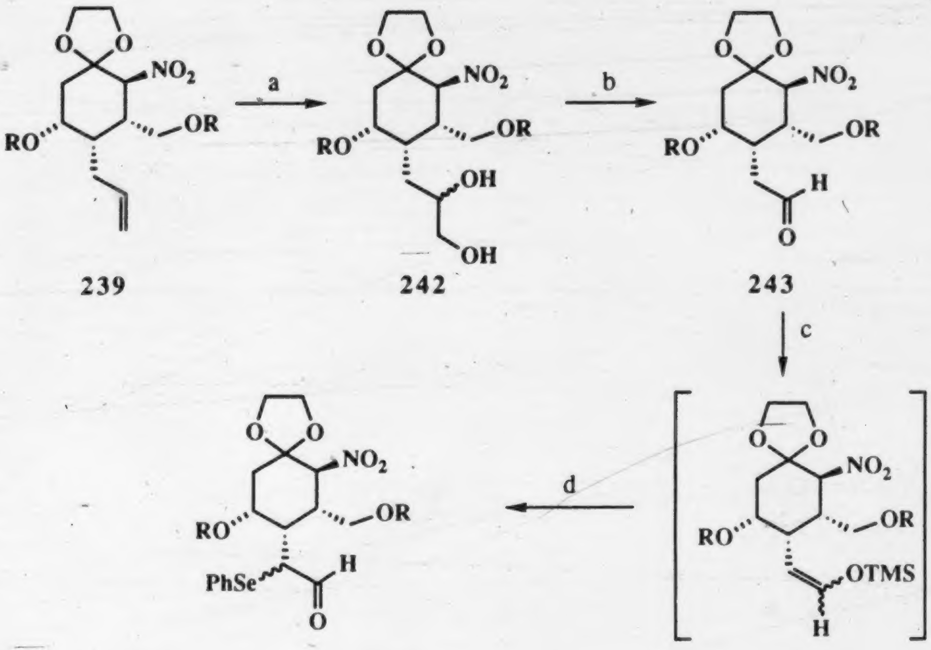
Eq. 15

It was not clear, however, if the selenenylation would be stereoselective, and if so, what the nature and extent of the preference would be. However, **239** certainly offered an asymmetric environment that was worth exploiting.

Conversion of **239** to diols **242** by osmylation, followed by cleavage using sodium periodate, afforded aldehyde **243** in 82% overall yield (scheme 39). Conversion to the silyl enol ethers **244a** and **244b**, and quenching *in situ* with an excess of benzeneselenenyl chloride (-20 °C) afforded the corresponding selenides **245a** and **245b** in a ratio of 4:1 (92%). The stereochemistry of the selenides was assigned on the basis of the results that were later obtained with **254a** and **254b** (see later).

The environment offered by **243** therefore does favor one isomer over the other and the selectivity is probably acceptable, but the major compound is the undesired isomer.

SCHEME 39



239 242 243

245a α - PhSe
245b β - PhSe

244a (*Z*) enol ether
244b (*E*) enol ether

R = TBDMS

Scheme 39. Reagents and conditions: (a) OsO_4, NMMO, acetone-water; (b) $NaIO_4$, MeOH, 82% overall; (c) TMSCl, Et_3N, $ZnCl_2$, PhH; (d) add PhSeCl at -20 °C, ratio **245a**:**245b**::4:1, 92% overall.

Isolation and analysis by ^{1}H NMR of the intermediate silyl enol ethers **244b** and **244a** shows an 8:1 mixture (^{1}H NMR) of (*E*) and (Z) isomers, respectively. It is interesting to note that although, under thermodynamic conditions, simple aldehydes give mainly the (Z) enol ether (7:3 in the case of butanal),[58] **243** behaves differently. More interesting though is the result obtained when a small amount of the (Z) enol ether **244a** was isolated by flash chromatography and treated with benzeneselenyl chloride (-20 °C).

The major seleno aldehyde was now the desired one (**245b**:**245a**::8:1) and the interpretation of this outcome is, of course, that the (*Z*) enol ether **244a** leads mainly to the desired selenide **245b** whereas the (*E*) isomer leads to the undesired **245a**.

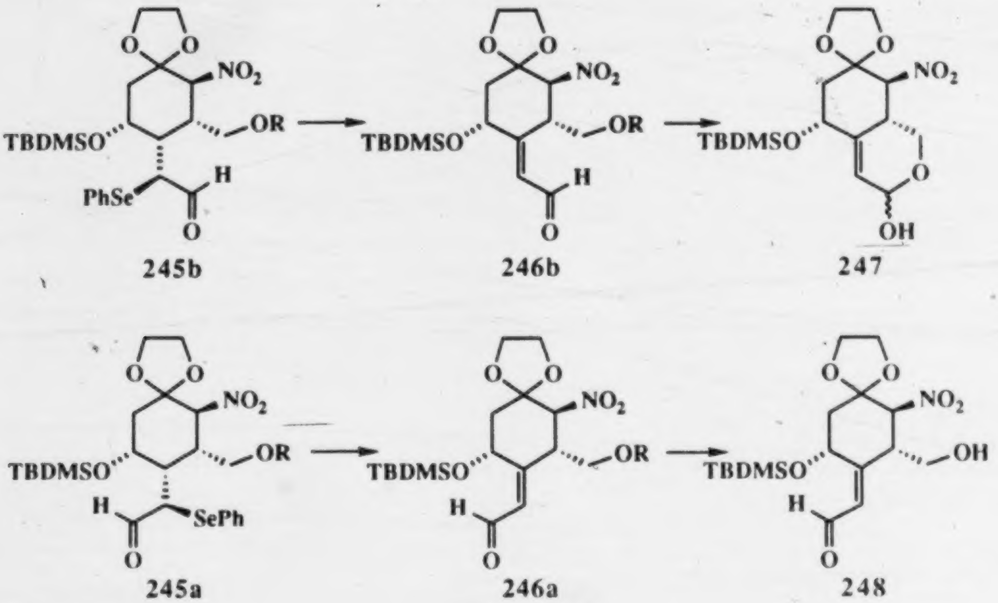
Attempts to get a high proportion of (*Z*) enol ether failed, the best result being **244b**:**244a**::2:1, and, therefore, this strategy was put aside. Before doing so, it was necessary to ensure that the stereochemistry indicated for the selenides **245a** and **245b** was correct and the assignment was established as follows:

After conversion of the selenides to the corresponding α,β unsaturated aldehydes (Scheme 40), selective deprotection of the primary alcohol will lead, in one case, to lactols **247** which, of course would have no aldehyde signals in the ^{1}H NMR spectrum, and in the other case to aldehyde **248**. The presence or the absence of an aldehyde signal in the ^{1}H NMR spectrum would therefore indicate the geometry of the double bond and, by correlation, the stereochemistry of the selenides.

It was decided to conduct this study on the triethylsilyl urethane derivative **249** because, in the event that the stereoselectivity can be forced to favor the desired isomer - a possibility not yet established - the chemistry developed could be employed for further elaboration directly towards calicheamicinone. It should also be pointed out that preliminary results had indicated that selective deprotection of the primary alcohol in the bis-*t*-

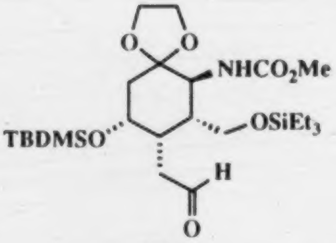
butyldimethylsilyl series was not efficient enough. Hence the more labile triethylsilyl derivative was prepared as described later.

SCHEME 40



TBDMSO
NO$_2$
OR
PhSe
SePh
H
O
OH
245b
246b
247
245a
246a
248

R = t-BuMe$_2$Si or Et$_3$Si

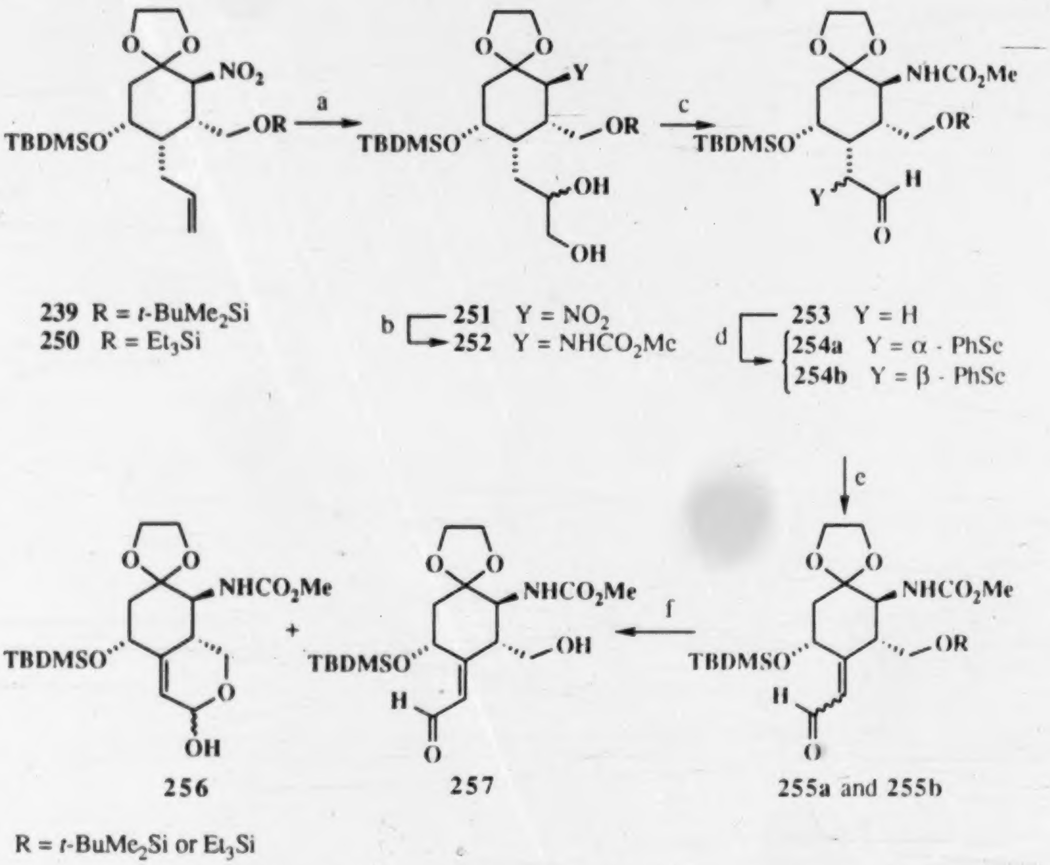


TBDMSO
NHCO$_2$Me
OSiEt$_3$
H
O

249

Olefin **250** (R = Et$_3$Si) was hydroxylated to **251** (R = Et$_3$Si) in 95% yield, ~~and~~ it was decided to hydrogenate the nitro group to an amine function at this stage (Scheme 41). The diol plays the role of masking the double bond and so protects it against hydrogenation. It also serves as a handle for producing the aldehyde **253**. In the event, this apparently simple hydrogenation required a very great effort extending over several months.

SCHEME 41

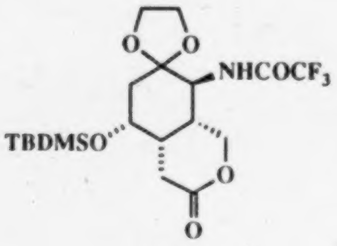

NO2
a
OR
TBDMSO
Y
OH
OH
c
NHCO2Me
H
O
239 R = t-BuMe2Si
250 R = Et3Si
b
251 Y = NO2
252 Y = NHCO2Me
d
253 Y = H
254a Y = α - PhSe
254b Y = β - PhSe
e
f
+
256
257
255a and 255b
R = t-BuMe2Si or Et3Si

Scheme 41. Reagents and conditions: (a) OsO_4, NMMO, acetone-water, 95%; (b) H_2, Raney Nickel, 2:1 ethanol-methanol; then $ClCO_2Me$, Et_3N, CH_2Cl_2, -30 °C, 45% overall; (c) $NaIO_4$, MeOH, 65%; (d) TMSCl, Et_3N, PhH followed by addition of PhSeCl at -20 °C, ratio **254a**:**254b**::3:1; (e) 30% aqueous H_2O_2 (6 equiv), pyridine (12 equiv), CH_2Cl_2-THF, ratio **255a**:**255b**::7:3, 39%; (f) TFA (3 equiv), THF-water, ratio **257**:**256**::7:3.

Eventually, it was found that treatment of **251** (R = Et_3Si) with Raney Nickel under carefully adjusted conditions (see later) and conversion of the resulting crude amine to carbamate **252** (R = Et_3Si) could be achieved in 45% overall yield (Scheme 41). [The corresponding transformations in the bis-*t*-butyldimethylsilyl series (**251=242**, R = *t*-$BuMe_2Si$) were also performed and gave urethanes **252** (R = t-$BuMe_2Si$) in 55% yield.] Cleavage of diol **252** (R = Et_3Si) with sodium periodate gave the desired aldehyde **253** (R = Et_3Si) in 65% yield (85% for the bis-*t*-butyldimethylsilyl series). Surprisingly, the aldehyde was a mixture (3:1) of isomers. This was the cause for some concern for a long time but it was later established that the formation of a mixture was due only to rotational isomerism involving the urethane (see later). Selenenylation of **253** (R = Et_3Si) as before (the enol ethers could not be isolated) gave isomeric selenides **254a** and **254b** (R = Et_3Si) in a 3:1 ratio.[#] The corresponding ratio when R = *t*-$BuMe_2Si$ was 5.3:1. Conversion of **254a** and **254b** (R = Et_3Si) to unsaturated aldehydes **255a** and **255b** (R = Et_3Si) (3:1 ratio)[#] was achieved in modest yield (39%). (Again, the corresponding ratio when R = *t*-$BuMe_2Si$ was 5.3:1).[#] Treatment of the monotriethylsilyl derivative **255a** and **255b** (7:3 ratio)[#] with trifluoroacetic acid in cold (0 °C) aqueous THF gave cleanly **256** and **257** in approximately the same ratio[#] as the starting material. The signal from the minor aldehyde that was previously at δ 9.90 had dissapeared and the one corresponding to the major aldehyde was still present but had shifted slightly from δ 10.55 to δ 10.69. These results establish that the major isomer **245a** was the undesired one and therefore this approach for introduction of the double bond at C-13 and C-14 was abandoned.

[#] Each of the compounds was itself a mixture of (urethane) rotamers. For further discussion see p 201]

The next strategy explored to control the stereochemistry of the tail is one that uses some inherent features of the molecule itself, because it was planned to tie the tail to the hydroxymethylene group to form a lactone. Compound **258** became, therefore, the immediate goal. It has a number of potentially useful features, as will become clear.



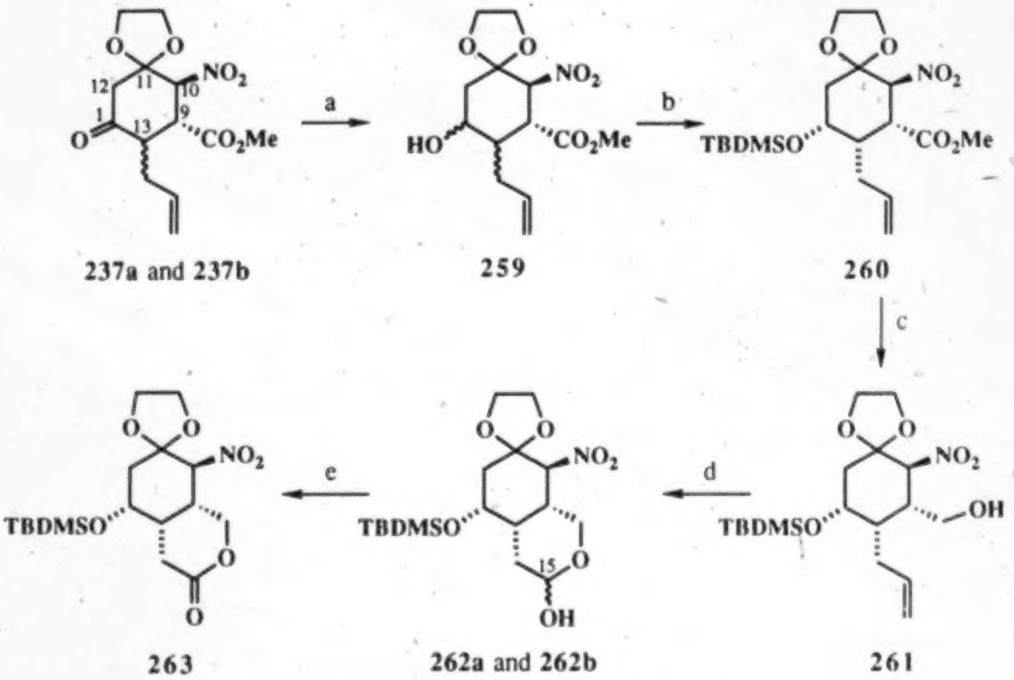
258

Compound **258** was synthesized from the Diels-alder adducts **237a** and **237b** as follows:

Treatment of **237a** and **237b** (83:17) with sodium borohydride (97%) produced a mixture of three isomeric alcohols **259** which could be silylated in excellent yield provided that the silylating agent (*t*-butyldimethylsilyl triflate) was added immediately after injection of 2,6-lutidine (Scheme 42). Failure to do so resulted mostly in recovery of starting material which would not react further even on addition of more reagent. The mixture of the three isomers was chromatographed, after which **260** was isolated (63%) and the remaining two isomers (25%) were left aside. The stereochemistry shown for **260** was determined on the basis of its ^{1}H NMR spectrum. The $C\underline{H}CO_2Me$ resonated at δ 3.52 (dd, J = 12.0, 4.5 Hz) and showed a large (axial-axial) coupling with $C\underline{H}NO_2$ and a small (equatorial-axial) coupling with C$\underline{H}$-allyl. The $C\underline{H}OSiR_3$

resonated at δ 4.06 (dt, J = 8.0, 5.0 Hz) and showed a large (axial-axial) coupling with both CH_2 and CH-allyl, as well as a small (equatorial-axial) coupling with one of the CH_2 hydrogens.

SCHEME 42


237a and 237b
259
260
261
262a and 262b
263
a
b
c
d
e
NO2
CO2Me
HO
TBDMSO
OH
12
11
10
9
1
13
15

Scheme 42. Reagents and conditions: (a) $NaBH_4$, CH_2Cl_2-MeOH, -78 °C to room temperature, 97%; (b) TBDMSOTf, lutidine, CH_2Cl_2 followed by separation, 63%; (c) DIBAL-H, CH_2Cl_2, -30 °C, 87%; (d) OsO_4, $NaIO_4$, *t*-butanol-THF-water, 98%; (e) PCC, CH_2Cl_2, 77%.

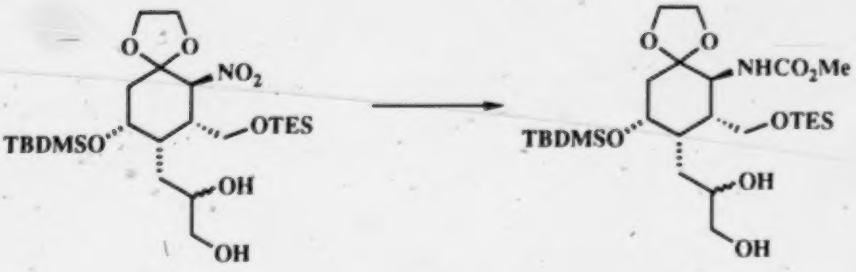
Ester **260** was converted (diisobutylaluminium hydride, -30 °C) to alcohol **261** in good yield (87%) providing that inverse addition of starting material to a cold (-30 °C) solution of the hydride was used. When the reducing agent was added to the substrate, the reaction proceeded only to a slight extent and mainly starting material was recovered.

We have no firm explanation for this unusual behavior, although we suspect that the nitro group, which confers a relatively high acidity to the adjacent hydrogen, is responsible.

The terminal double bond of compound **261**# was cleaved (osmium tetroxide, sodium periodate) to provide lactols **262a** and **262b** (98%) as a mixture of epimers at C-15. Oxidation of **262a** and **262b** with PCC gave lactone **263** in good yield (77%). This now appeared as the appropriate stage to attempt reduction of the nitro group to an amine for reasons that will become clear after the following observations.

Preliminary results had indicated that the previously discussed hydrogenation of the nitro derivative **251** (Equation 16) over Pd/C did not seem to proceed at all. Many attempts using many combinations of a wide variety of catalysts, pressure, reducing agents and substrates, all led to decomposition, or recovery (50–100%) of starting material.

# In a separate study, alcohol **261** was converted to its silyl ether **250** (Scheme 41) and shown to display a ^{1}H NMR spectrum identical (except for the Et_3Si signals) to the corresponding *t*-$BuMe_2Si$ derivative **239**, which was synthesized, as previously mentioned, from **237a** by reduction with diisobutylaluminium hydride followed by silylation. This observation therefore leads to the conclusion that both routes i.e. **237a** (page 188) to **239** (page 190) and **237a** to **260** (Scheme 42) to **250** (Scheme 41) afford the same stereoisomer.



251 **252** Eq. 16

A possible way to avoid the problem of the hydrogenation step was to attempt either sulfenylation α to the nitro group (so as to generate a ketone by hydrolysis) or direct oxidation of the nitro group to a ketone (Nef reaction), but experiments to implement such plans were unsuccessful.

We therefore tried hydrogenation again and it was eventually found after much effort that reduction of **251** to the corresponding amines followed by conversion to the derived urethanes **252** (see footnote page 201), worked in modest and fairly reproducible yields (45%), provided that a specific procedure was followed.

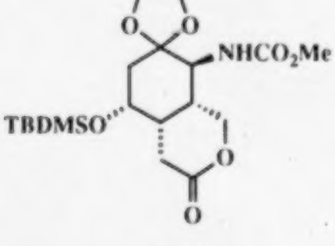
A 7:1 w/w ratio of freshly (< 1 week) prepared Raney Nickel (T-1 grade)[#] that had been thoroughly washed free of bases had to be used under a modest (50 psi) pressure of hydrogen, and methanol was required to solubilize the starting material sufficiently to allow good contact with the catalyst. When less catalyst was used many side products were formed; using more catalyst gave a clean reaction but recovery of material was drastically lowered. Presumably this was due to adsorption of the amine on the catalyst.

[#] See experimental

A way to minimize adsorption of amine on the catalyst had to be found, and so conversion of the very polar diol unit into a lactone was examined, and this is why the previously discusssed lactone **263** seemed suitable. Hydrogenation of nitro lactone **263** was attempted and, although the conditions that had been optimized for **251** were used, the results were, unfortunately, not promising enough to warrant further investigation. Poisoning of the catalyst still seemed to take place.

In a final attempt to overcome the problems, it was decided to try hydrogenation on the protected lactol **266** (Scheme 43).

It will be noted that the urethanes **252** were a mixture of isomeric diols. We suspected that (urethane) rotamers were involved as well, and this was confirmed as follows. The mixture of isomers **252** was converted in three steps to urethane-lactone **264**. At this point the ^{1}H NMR spectrum still showed a 3:1 mixture of isomers as evidenced by the presence of two singlets (COOMe) at δ 3.69 and δ 3.70. However, The ^{1}H NMR spectrum of the same sample heated at 50 °C significantly simplified (only one singlet at δ 3.70) and this led to the conclusion that the compound exists as two isomers arising from the restricted rotation about the NH–CO_2Me bond of the urethane unit.

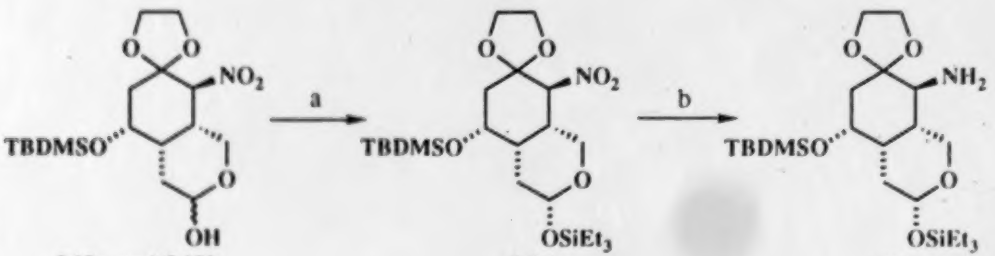


264

Silylation of lactols **262a** and **262b** gave **266** as a single isomer in 96% yield. The ^{1}H NMR spectrum showed that C$\underline{H}$OSiEt$_3$ resonated at δ 4.67 (dd, J = 9.0, 2.2 Hz). There was a large (axial-axial) coupling as well as a small (axial-equatorial) coupling with CH$_2$. Hence, the triethylsilyloxy group is equatorial, i.e. α.

Hydrogenation of **266** under the usual conditions [carefully washed Raney Nickel T-1, H$_2$ (50 psi)] gave the desired amine **267** in 89% yield!

SCHEME 43



262a and **262b** **266** **267**

Scheme 43. Reagents and conditions: (a) Et$_3$SiCl, Et$_3$N, DMAP, CH$_2$Cl$_2$, 96%; (b) H$_2$, Raney Nickel, ethanol-methanol, 89%.

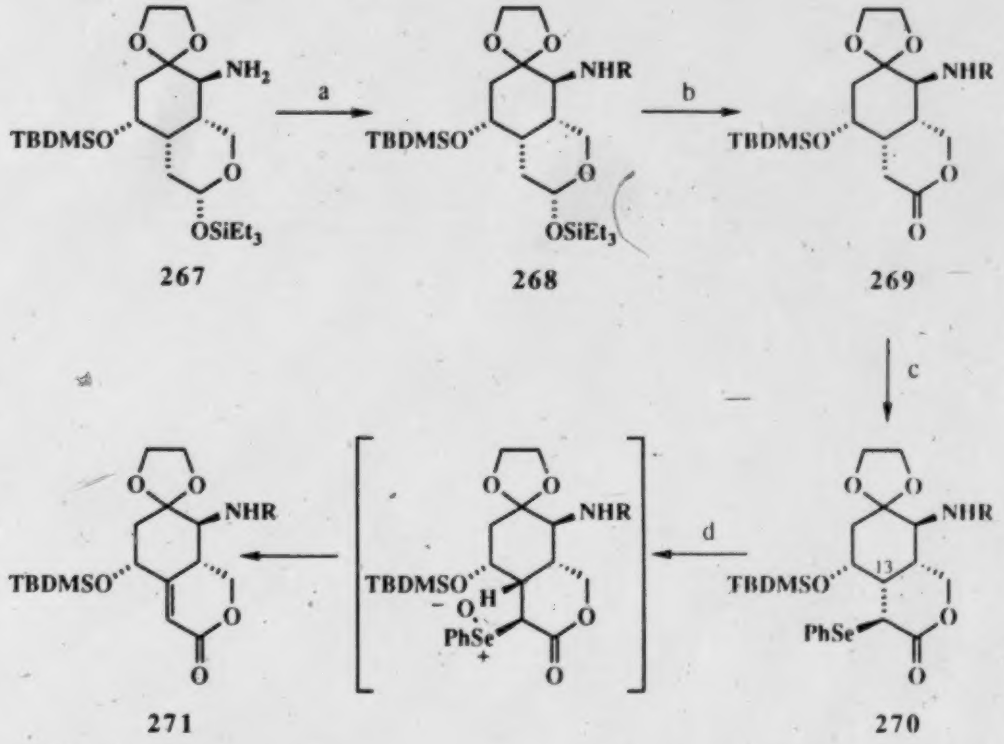
At long last, efforts could now be concentrated on elaboration of the amine into more advanced intermediates, and two routes were investigated.

2) Studies on elaboration of amine 267

(a) First route

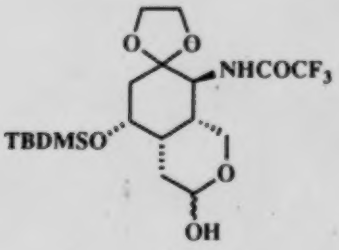
In the first route, amine **267** was cleanly converted (trifluoroacetic anhydride, pyridine, -30 °C) to carbamate **268** (R = $COCF_3$) (*ca.* 75%) along with a small amount of the corresponding lactols **268'**(*ca.* 10%) (Scheme 44 and page 204). (When the reaction was carried out at 0 °C to room temperature, only the lactols were obtained). The products **268** and **268'** were purified (SiO_2) and combined for the next step.

SCHEME 44


NH$_2$
TBDMSO
OSiEt$_3$
267
a
NHR
TBDMSO
OSiEt$_3$
268
b
NHR
TBDMSO
269
c
NHR
TBDMSO
13
PhSe
270
d
NHR
TBDMSO
H
O
PhSe
+
NHR
TBDMSO
271

R = CO_2Me or $COCF_3$

Scheme 44. Reagents and conditions: (a) TFAA, DMAP, pyridine, -30 °C; (b) PCC, CH_2Cl_2, 85% overall; (c) LDA, -78–0 °C, 30 min, followed by addition of PhSeBr at -78 °C, 64%; (d) 30% aqueous H_2O_2, pyridine, CH_2Cl_2-THF, 92%.



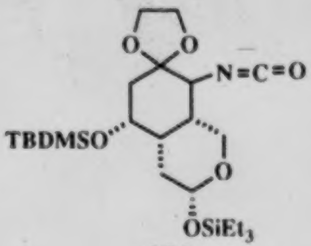
268'

PCC oxidation of the mixture gave lactone **269** (R = $COCF_3$) in 85% yield overall yield. It will be noted that prior removal of the triethylsilyl group is not necessary as it is lost under the reaction conditions, to give the corresponding lactols **268'** which are oxidized to the lactone.

Compound **269** was converted cleanly to the selenide **270** in 64% yield. As expected, attack of benzeneselenyl bromide proceeded from the less hindered face of the molecule, i.e. the β-face. Moreover, the newly introduced phenylseleno group is *syn* to the hydrogen to be abstracted at C-13. Oxidation gave the corresponding selenoxide and this collapsed easily to the desired α,β-unsaturated lactone **271** in excellent yield (92%). It will be noted that by using this strategy, the geometry of the double bond has been totally controlled in the desired sense.

The reason why carbamate **269** (R = $COCF_3$) as opposed to urethane **269** (R = CO_2Me) was used is because selenenylation of the latter [synthesized from amine **267** using the same type of route as the one used for the carbamate**269** (R = $COCF_3$) (Scheme 44)] under similar conditions, gave the desired selenide **270** (R = CO_2Me) only in poor yield (30%).

The urethane moiety was suspected to be directly responsible for the low yield based on the following observations. Conversion of amine **267** to the corresponding urethane **268** (R = CO_2Me) (methyl chloroformate, triethylamine) gave variable results depending on the exact conditions. Invariably only a little (*ca*. 15%) of the desired urethane was formed, and instead a relatively very non-polar compound (TLC), that was somewhat unstable to silica, was isolated. It was identified as isocyanate **272**.



272

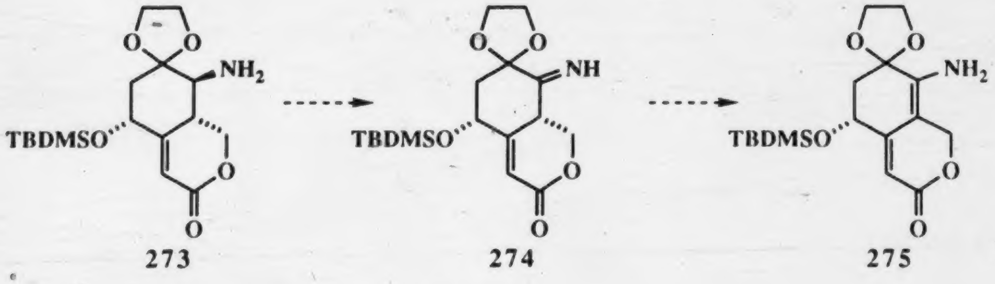
Clearly, the urethane moiety had a tendency to eliminate methanol and, therefore, it was no surprise, that some complications arose when the urethane **269** (R = CO_2Me) was subjected to strongly basic (lithium diisopropylamide) conditions in the selenenylation step.

The carbamate function, however was satisfactory, and it had the advantage of being potentially easily removed under mild conditions (methanolic potassium carbonate).[59]

Therefore, once the unsaturated lactone was introduced, we had planned to remove the protecting group to give the amine **273** (Scheme 45).

Oxidation of the amine to the imine would be followed by tautomerization to the target enamine **275**.

SCHEME 45



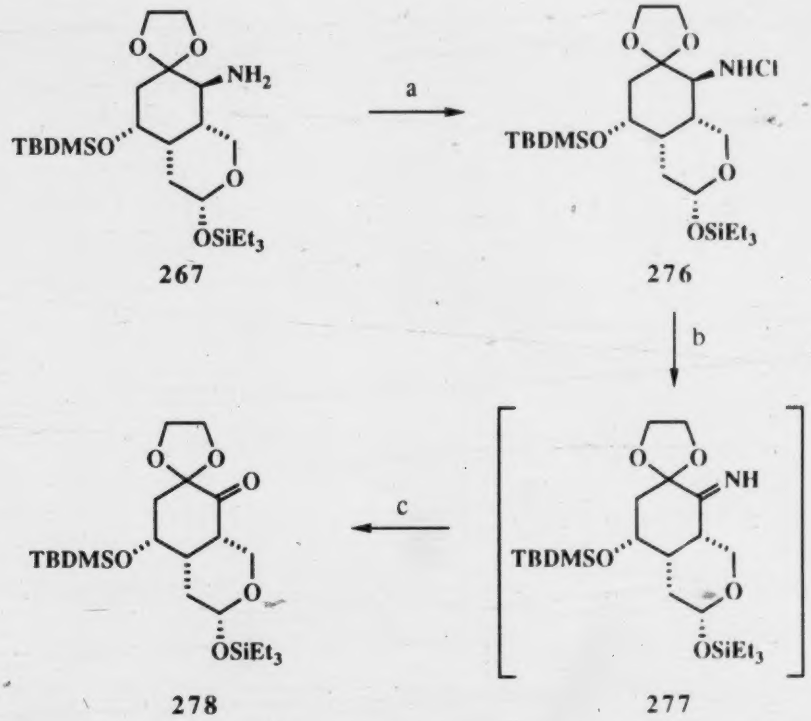
Unfortunately, the protecting group was more resistant than expected, and preliminary attempts to remove it under less mild conditions (methanolic sodium hydroxide) did not result in formation of the desired amine **273**, or of any identifiable product. Quite certainly the complications arise from the fact that the lactone portion is affected by these conditions. For this reason, the approach involving the carbamate was temporarily set aside and a second approach was investigated.

(b) Second route

Our plan was to try to generate the enamine portion and *then* to generate the unsaturated lactone. Attempts to convert amine **267** to ketone **278** in one operation (sodium hypochlorite, phase transfer conditions),[60] were not successful (Scheme 46). Such experiments led to the formation of a mixture of monochloroamine **276** and its dichloro analog. The conversion was, however, achieved in two steps.

Treatment of **267** with 1.0 equiv of *tert*-butylhypochlorite gave the monochloride **276** in 77% yield and treatment of **276** with DBU gave presumably the imine **277**. This was not isolated but underwent hydrolysis to ketone **278** (87%) (ν_{max} C=O 1738 cm^{-1}), which was the compound actually obtained.

SCHEME 46


NH₂
TBDMSO
OSiEt₃
267
a
NHCl
TBDMSO
OSiEt₃
276
b
NH
TBDMSO
OSiEt₃
277
c
TBDMSO
OSiEt₃
278

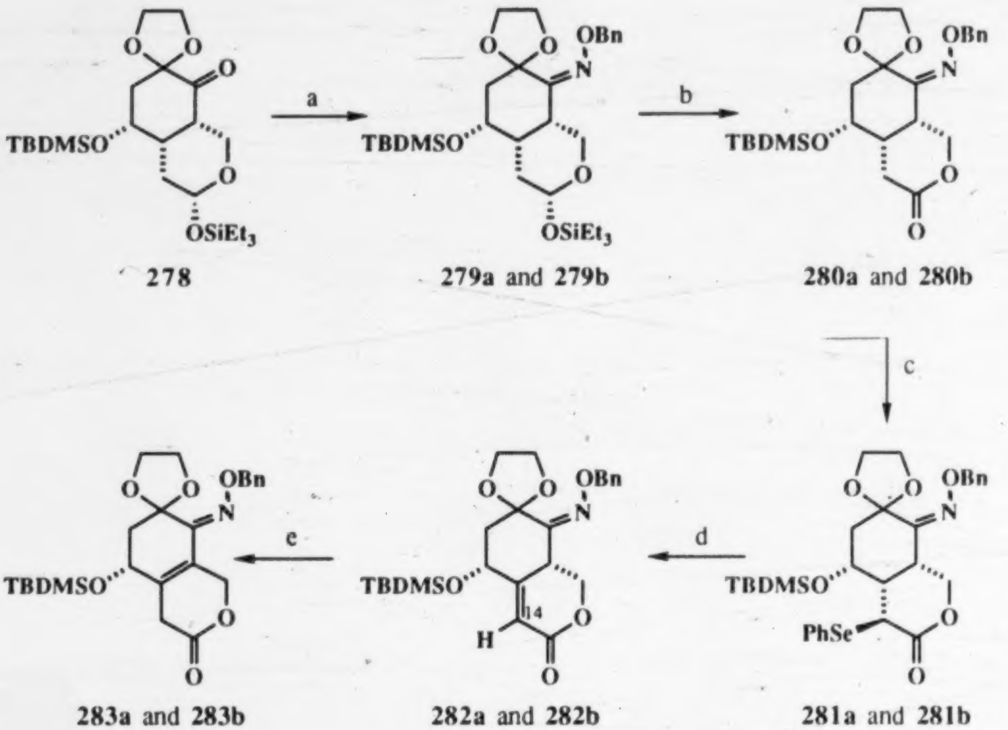
Scheme 46. Reagents and conditions: (a) *t*-BuOCl, THF-Et_2O, -45 °C, 77%; (b) DBU, $PhCH_3$, 100 °C, 2 h; (c) aqueous NH_4Cl, 15 min, 87% overall.

Some imines had been converted to their corresponding enamides (acetic anhydride, 160 °C, acid)# but we had other plans in mind.

# For a review on preparation and photochemistry of enamides, see reference 61.

Ketone **278** was converted to the stable oxime derivatives **279a** and **279b** in good yield (75%, ratio 1:1) (Scheme 47).

SCHEME 47


a
b
c
d
e
TBDMSO
OSiEt₃
OBn
N
PhSe
H
14
278
279a and 279b
280a and 280b
281a and 281b
282a and 282b
283a and 283b

Scheme 47. Reagents and conditions: (a) $BnONH_2$.HCl, pyridine, EtOH, molecular sieve 4 Å, 75%; (b) PCC, CH_2Cl_2, 90%; (c) LDA, -78 °C, 90 min followed by addition of PhSeBr at -78 °C, 82%; (d) dimethyl dioxirane in acetone, *ca* 100% crude; (e) SiO_2

Gratifyingly, the triethylsilyl group resisted to a very large extent (but not completely) these conditions. Oximes have also been converted to enamides (acetic anhydride, pyridine, 160 °C),[61] but we planned to attempt this transformation later , as our oxime functionality represents a suitable protecting group for nitrogen while we elaborate the lactone moiety.

It will be noted that so far, in this series of transformations, not only the nitrogen functionality was reintroduced but a new unsaturation was created.

PCC oxidation of **279a** and **279b** gave **280a** and **280b** directly in excellent yield (90%) (ν_{max} C=O 1737 cm^{-1}). Selenenylation of **280a** and **280b** in the presence of the now suitably protected nitrogen, then afforded **281a** and **281b** in 82% yield. The success of this last transformation was most pleasing because we did not know beforehand if deprotonation (lithium diisopropylamine) would take place α to the lactone or α to the oxime. Lithium diisopropylamide has been used previously for generation of enolates of both oximes and lactones; we were not aware, however, of any examples where generation of the enolate of one functionality had been selectively achieved in the presence of the other.

We then proceeded to the next step and, surprisingly, oxidation of **281a** and **281b** (*m*-chloroperbenzoic acid or 30% hydrogen peroxide) followed by flash chromatography gave very little of the desired compound **282a** and **282b**, as evidenced by the absence of the typical triplet at δ 6.15, which corresponds to the vinyl hydrogen at C-14. Oxidation of **281a** and **281b** with sodium periodate in THF, and analysis of the crude mixture (^{1}H NMR) showed what could be identified as the desired compounds, but the latter were contaminated with unidentified byproducts. Attempts to purify the desired lactones **282a** and **282b** by flash chromatography led to recovery of the same material that was observed when *m*-chloroperbenzoic acid or 30% hydrogen peroxide had been used as oxidizing agent.

We therefore came to the conclusion that the desired material was unstable to silica, and so purification was avoided by oxidizing **281a** and **281b** with dimethyl dioxirane in acetone (-78 °C to room temperature). This operation gave cleanly (107% crude yield, > 95 mol% pure by ^{1}H NMR) the desired α,β-unsaturated lactone **282a** and **282b**. The ^{1}H NMR spectrum showed a mixture of two isomeric oximes in a 1:1 ratio with the vinylic hydrogen of the isomers resonating at δ 6.15 (t, J = 2.2 Hz) and δ 6.12 (t, J = 2.2 Hz), respectively. The ^{13}C NMR spectrum had the expected number of signals in the C=C region and the IR spectrum showed a strong absorption at 1733 cm^{-1}, characteristic of an α,β-unsaturated lactone.

When this material was left in contact with silica gel for 15 min and then subjected to flash chromatography, it was converted cleanly to isomers **283a** and **283b**. The structure is tentatively assigned, mainly on the basis of the disappearance of the vinylic signals in the ^{1}H NMR spectrum, the infrared absorption at 1748 cm^{-1}, which indicates the presence of a lactone that is not α,β-unsaturated, and on the basis of the observation of the expected ion $(M - C_4H_9)^+$ in the high resolution mass spectrum.

--Conclusion--

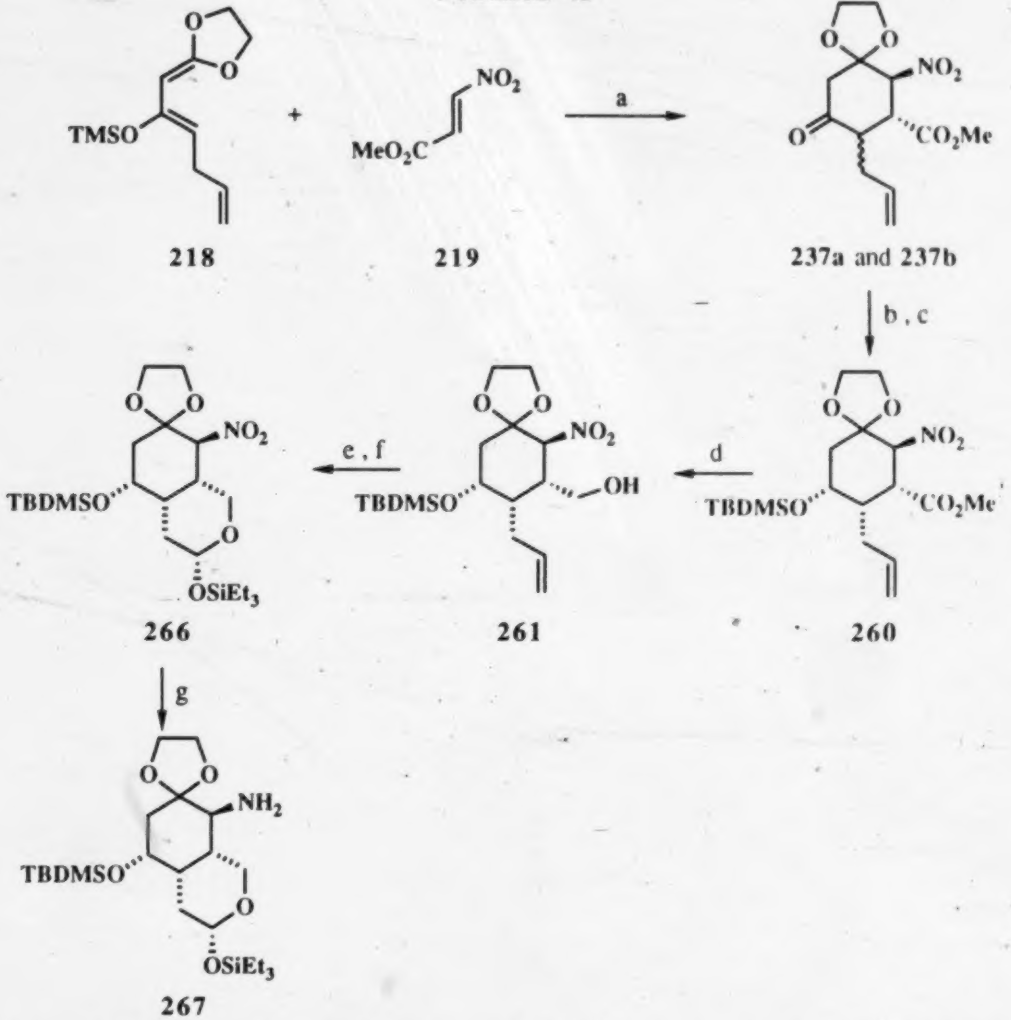
This section of the thesis describes:

a) The preparation of a novel diene and its successful use in a Diels-Alder reaction.

b) The construction of a potential precursor to the central core of calicheamicinone.

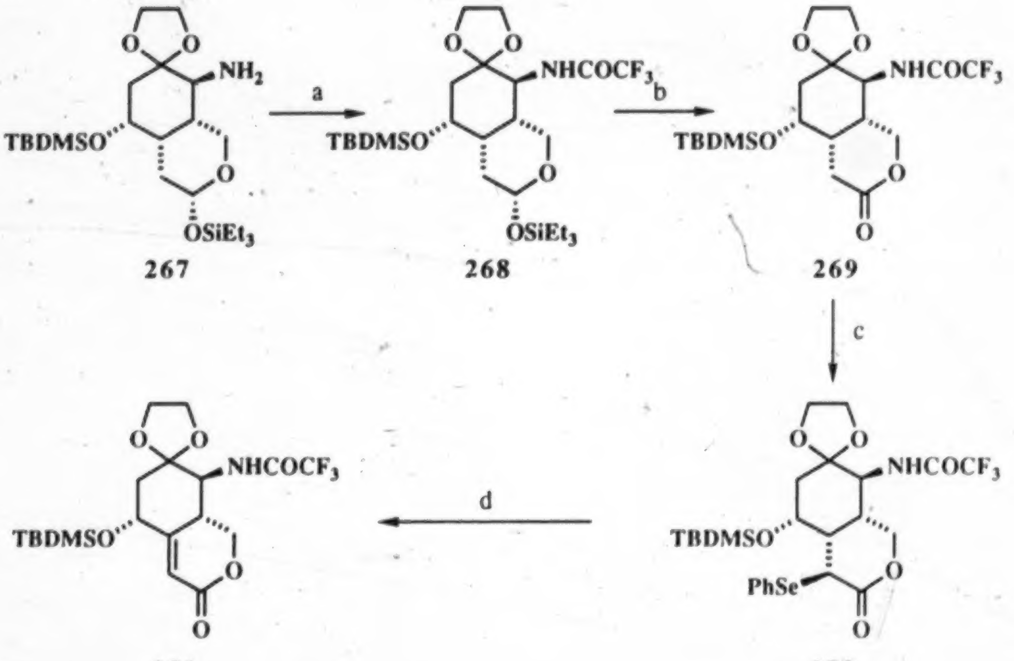
c) Elaboration of this precursor to a level where both unsaturations necessary for preparation of the diene moiety have been introduced. The geometry of the double bond at C-13 and C-14 is controlled and, in a very few steps, an advanced intermediate suitable for coupling with dilithioenediyne should be accessible. A resume of the two most promising routes is shown in (Scheme 48 to 50).

SCHEME 48


TMSO
218
+
NO2
MeO2C
219
a
O
NO2
CO2Me
237a and 237b
b, c
TBDMSO
NO2
CO2Me
260
d
OH
261
e, f
OSiEt3
266
g
NH2
267

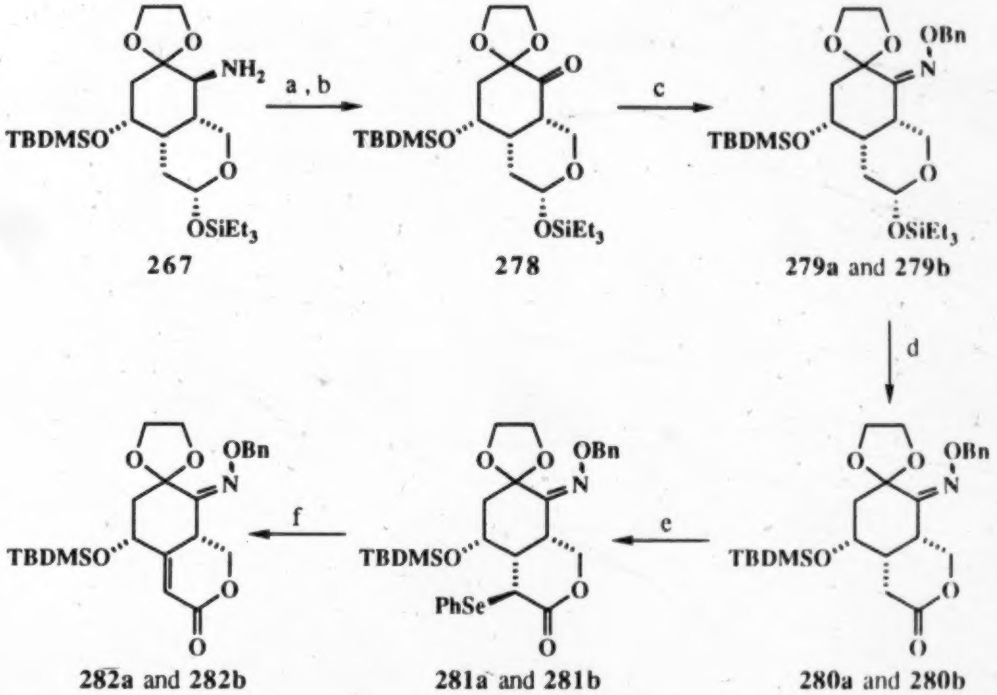
Scheme 48. Reagents and conditions: (a) neat, 0 °C, 1 h; then mild acid; (b) $NaBH_4$, CH_2Cl_2-MeOH, -78 °C to room temperature, 97%; (c) TBDMSOTf, lutidine, CH_2Cl_2, followed by separation, 63%; (d) DIBAL-H, CH_2Cl_2, -30 °C, 87%; (e) OsO_4, $NaIO_4$, *t*-butanol-THF-water, 98%; (f) Et_3SiCl, Et_3N, DMAP, CH_2Cl_2, 96%; (g) H_2, Raney Nickel, ethanol-methanol, 89%.

SCHEME 49


TBDMSO
NH$_2$
OSiEt$_3$
267
a
NHCOCF$_3$
268
b
269
c
270
PhSe
d
271

Scheme 49. Reagents and conditions: (a) TFAA, DMAP, pyridine, -30 °C; (b) PCC, CH_2Cl_2, 85% overall; (c) LDA, -78 °C to 0 °C, 30 min, followed by addition of PhSeBr at -78 °C, 64%; (d) 30% aqueous H_2O_2, pyridine, CH_2Cl_2-THF, 92%.

SCHEME 50

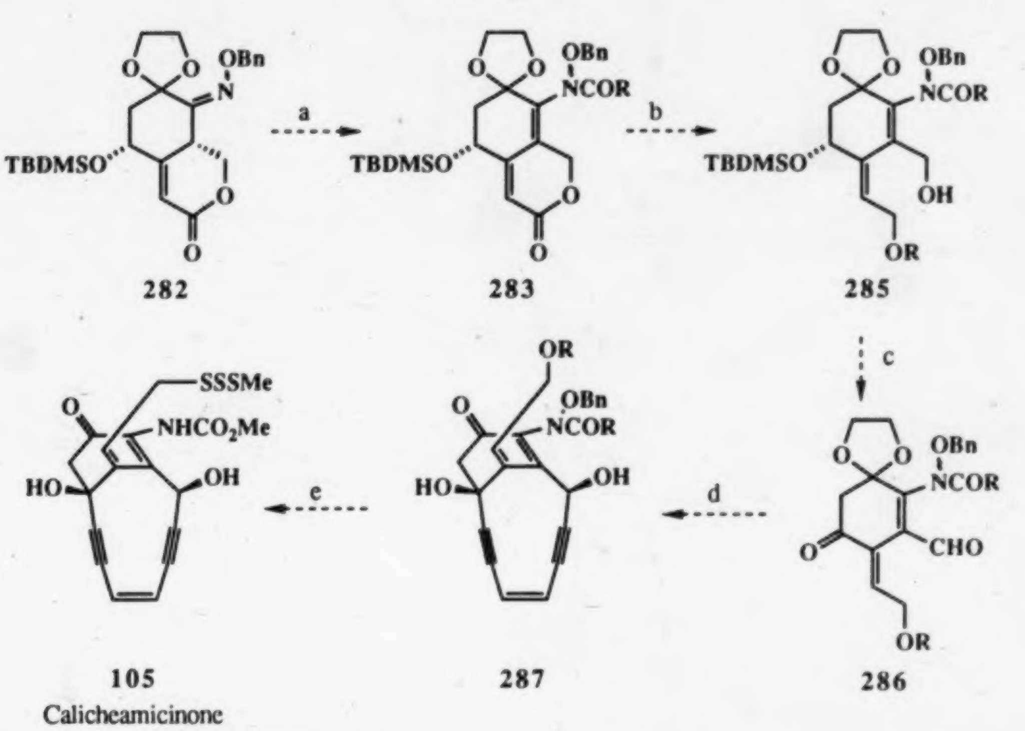


NH2
O
TBDMSO
OSiEt3
267
a , b
278
c
OBn
N
279a and 279b
d
280a and 280b
e
PhSe
281a and 281b
f
282a and 282b

Scheme 50. Reagents and conditions: (a) *t*-BuOCl, THF-Et_2O, -45 °C, 77%; (b) DBU, $PhCH_3$, 100 °C, 2 h, followed by aqueous NH_4Cl, 15 min, 87%; (c) $BnONH_2$.HCl, pyridine, EtOH, 4 Å molecular sieves, 75%; (d) PCC, CH_2Cl_2, 90%; (e) LDA, -78 °C, 90 min, followed by addition of PhSeBr at -78 °C, 82%; (f) dimethyl dioxirane in acetone, *ca* 100% crude.

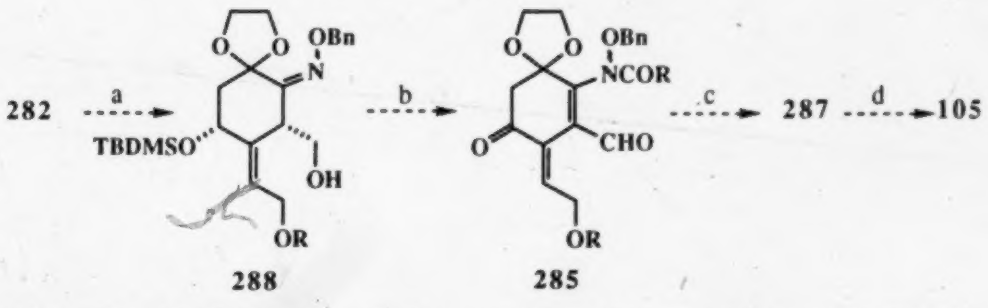
On the basis of our findings, the following synthetic routes (among others) suggests themselves (Scheme 51 and 52). Which route is the most promising is impossible to evaluate at this point since the behavior of the intermediates involved in the project so far were shown to be most unpredictable. Work currently underway in our laboratory will provide the necessary information.

SCHEME 51


OBn
N
TBDMSO
O
282
a
NCOR
283
b
OH
OR
285
c
CHO
286
d
287
e
SSSMe
NHCO₂Me
HO
OH
105
Calicheamicinone

Scheme 51. (a) RCOCl; (b) (i) H⁻, (ii) selective protection; (c) (i) removal of TBDMS group, (ii) oxidation; (d) dilithioenediyne; (e) (i) N-O cleavage (e.g., Zn-Cu[62a] or Ra-Ni[62b]), (ii) introduction of the trisulfide moiety.[34]

SCHEME 52

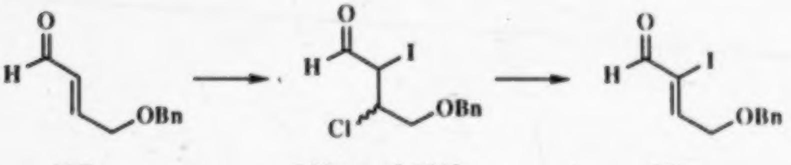

282
a
OBn
N
TBDMSO
OH
OR
288
b
NCOR
CHO
285
c
287
d
105

Scheme 52. (a) (i) H⁻, (ii) selective protection; (b) (i) oxidation, (ii) RCOCl; (c) dilithioenediyne; (d) (i) N-O cleavage (e.g. Zn-Cu[62a] or Ra-Ni[62b]), (ii) introduction of the trisulfide moiety.[34]

III. EXPERIMENTAL

The general remarks made in Chapter 1 apply:

(Z)-2-Iodo-4-(phenylmethoxy)-2-butenal (182).

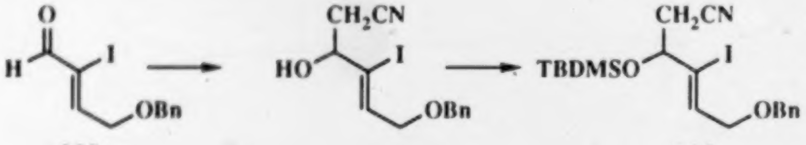


197 **198a** and **198b** **182**

(a) 3-Chloro-2-iodo-4-(phenylmethoxy)-2-butanal (198a and 198b). Mercuric chloride[48] (16.94 g, 62.4 mmol) was added in one portion to a well stirred and cooled (0 °C) solution of iodine (31.67 g, 124.8 mmol) in dichloromethane (250 mL). The mixture was stirred for 15 min, and aldehyde[47] **197** (10.9 g, 61.8 mmol) was added in one portion. The resulting suspension was then stirred at room temperature for 3 h. The red precipitate was filtered off and the filtrate was washed with 10% w/v aqueous sodium thiosulfate (2 x 100 mL), and water (1 x 50 mL), and dried ($MgSO_4$). Evaporation of the solvent gave crude **198a** and **198b** (19.25 g) which was used directly for the next step.

(b) (Z)-2-Iodo-4-(phenylmethoxy)-2-butenal (182). The reaction mixture was protected from light by wrapping the reaction flask with aluminum foil. Potassium acetate (7.66 g, 78 mmol) was added in one portion to a cold (0 °C) and stirred solution of crude **198a** and **198b** (17.6 g) in glacial acetic acid. The cold bath was removed and the mixture was stirred at room temperature for 16 h. Dichloromethane (400 mL) was added followed by carefull addition of saturated aqueous sodium bicarbonate (1 x 400 mL). The aqueous layer was extracted with dichloromethane (2 x 300 mL) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (1 x 400 mL), and water (200 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (80 x 200 mm) using 15% ethyl acetate--hexane gave **182** (12.18 g, 71% from **197**) as a slightly yellow oil. The material could be kept in the freezer for several weeks without significant decomposition: FT-IR ($CHCl_3$ cast) 1700, 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.41 (d, J = 5.4 Hz, 2 H), 4.62 (s, 2 H), 7.29--7.40 (m, 5 H), 7.48 (t, J = 5.4 Hz, 1 H), 8.62 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 73.48, 73.66, 108.65, 127.95, 128.18, 128.63, 137.12, 158.53, 186.81; mass for $C_{11}H_{11}O_2I$ (chemical ionisation, NH_3) 320 $(M + 18)^+$. Anal. Calcd for $C_{11}H_{11}O_2I$: C, 43.73; H,.3.67; O, 10.59. Found: C,43.69; H,3.63; O, 10.85.

(Z)-3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-4-iodo-6-(phenylmethoxy)-4-hexenenitrile (199).

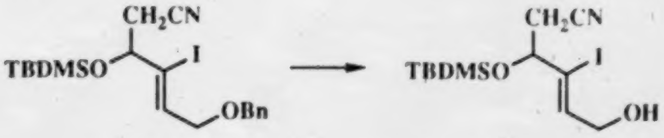


182 **199**

(a) (Z)-3-Hydroxy-4-iodo-6-(phenylmethoxy)-4-hexenenitrile. Dry acetonitrile (0.75 mL, 14.46 mmol) was added dropwise over 5 min to a cold (-78 °C) and stirred solution of LDA (13.74 mmol) in dry ether (50 mL). Stirring was continued for 30 min at -78 °C, and then a solution of iodo aldehyde **182** (2.5 g, 7.23 mmol) in ether (10 mL + 2 mL rinse) was added over 1 h (syringe pump) to the cold mixture. During the addition, a white precipitate formed. Stirring was continued for 15 min after the end of the addition, and the mixture was then poured into a separatory funnel containing ether (50 mL) and saturated aqueous ammonium chloride (20 mL). The aqueous layer was extracted with ether (30 mL), and the combined organic extracts were washed with 10% w/v aqueous sodium thiosulfate (1 x 30 mL), and water (1 x 30 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (40 x 200 mm) using 35% ethyl acetate--hexane gave the desired alcohol [2.0 g, 71% (79% based on conversion)] as a reddish oil.

(b) (Z)-3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-4-iodo-6-(phenylmethoxy)-4-hexenenitrile (199). Imidazole (1.74 g, 25.56 mmol) and *tert*-butylchlorodimethylsilane (1.85 g, 12.27 mmol) were added to a stirred solution of the above alcohol (1.90 g, 4.91 mmol) in dry DMF (10 mL). The mixture was stirred at 35 °C for 16 h and diluted with ether (120 mL). The resulting mixture was washed with water (2 x 30 mL), and the organic layer was dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (50 x 200 mm) using 10% ethyl acetate--hexane gave **199** (2.44 g, 99%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s) and 0.19 (s) [both signals together correspond to 6 H], 0.97 (s, 9 H), 2.58--2.79 (m, 2 H), 4.15--4.27 [m, including a d (J = 4.8 Hz) at δ 4.19, 3 H], 4.57 (s, 2 H), 6.45 (dt, J = 5.2 Hz, 1 H), 7.30--7.42 (m, 5 H).

(Z)-3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6-hydroxy-4-iodo-4-hexenenitrile (200).

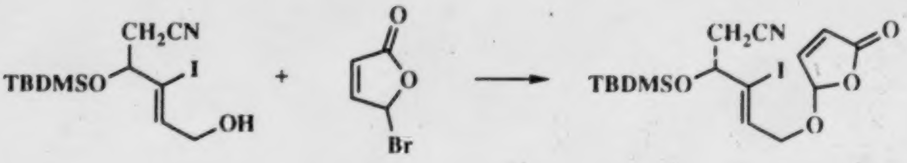


199 **200**

Boron tribromide (1 M in CH_2Cl_2, 550 mL, 0.55 mmol) was added over

1 min to a cold (-78 °C) stirred solution of **199** (238 mg, 0.52 mmol) in dry dichloromethane (5 mL). Stirring at 0 °C was continued for 45 min and the mixture was then quenched with saturated aqueous sodium bicarbonate (1 x 5 mL). The mixture was diluted with ether (1 x 15 mL), and the organic layer was washed with water (1 x 5 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (15 x 200 mm) using 35% ethyl acetate--hexane gave **200** (176 mg, 92%) as a white solid: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s) and 0.19 (s) [both signals together correspond to 6 H], 0.97 (s, 9 H), 1.74 (t, J = 5.6 Hz, 1 H), 2.70 (d, J = 6.0 Hz, 2 H), 4.22 (t, J = 6.0 Hz, 2 H), 4.31 (t, J = 5.6 Hz, 2 H), 6.45 (dt, J = 6.0, 0.8 Hz, 1 H).

(Z)-5-[[5-Cyano-4-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-3-iodo-2-pentenyl]oxy]-2(5H)furanone (193).

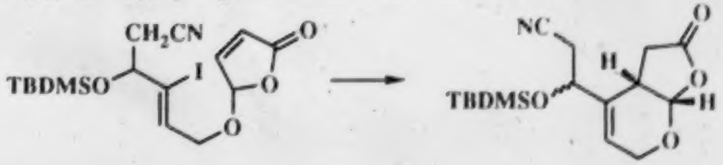


200 **201** **193**

(a) Silver triflate (806 mg, 3.14 mmol) in dry nitromethane (15 mL) and 2,4,6-collidine (0.389 mL, 2.94 mmol) in dry nitromethane (15 mL) were added simultaneously over 1 h (syringe pump) to a cold (0 °C) and stirred solution of **200** (807 mg, 1.96 mmol) and 5-bromo-2(5*H*)-furanone[49] **221** (476 mg, 2.94 mmol) in the same solvent (30 mL). The cold bath was removed and the mixture was stirred for 1 h, and then diluted with ether (150 mL). The resulting mixture was washed with water (2 x 40 mL), and the organic layer was dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (50 x 200 mm) using 35% ethyl acetate--hexane gave a 1:1 mixture of **200** and **193** (760 mg) which was used directly in the next experiment.

(b) *tert*-Butoxychlorodiphenylsilane[63] (0.542 mL, 2.03 mmol) and then DMAP (25 mg) were added to a stirred solution of **200** and **193** (760 mg) and triethylamine (0.281 g, 0.387 mL, 2.77 mmol) in dry dichloromethane (20 mL). Stirring at room temperature was continued for 1 h and the mixture was diluted with dichloromethane (30 mL). The resulting mixture was washed with saturated aqueous sodium bicarbonate (1 x 10 mL), water (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (25 x 200 mm) using 6% ethyl acetate--hexane gave pure **193** (438 mg, 50%) and the silyl ether derivative of **200** (323 mg, 24 %). Compound **193** had: FT-IR ($CHCl_3$ cast) 2240, 1798, 1782 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.10 (s) and 0.15 (s) [both signals together correspond to 6 H), 0.92 (s, 9 H), 2.6--2.78 (m, 2 H), 4.18--4.28 (m, 1 H), 4.30--4.50 (m, 2 H), 5.96--6.00 (m, 1 H), 6.26 (dt, J = 6.0, 1.0 Hz, 1 H), 6.39--6.47 (m, 1 H), 7.24 (dt, J = 5.6, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -5.13, -4.64, 17.97, 25.54, 26.98, 27.01, 72.69, 72.79, 74.82, 102.42, 102.47, 111.57, 111.94, 116.30, 116.35, 125.14, 125.17, 133.07, 133.20, 150.05, 170.00; exact mass, *m/z* calcd for $C_{15}H_{21}INO_4Si$ (M - CH_3)$^+$ 434.0284, found 434.0276.

3-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[2,3,3a,7a-tetrahydro-2-oxo-6*H*-furo[2,3-b]pyran-4-yl]propanenitrile (202a and 202b).

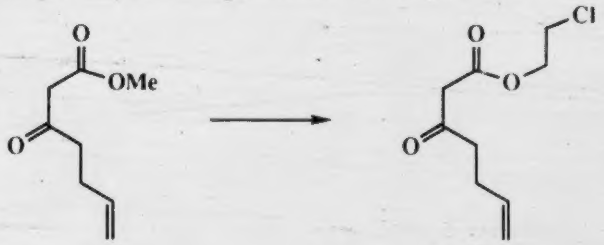


193 **202a and 202b**

Tributyltin hydride (22 mg, 0.076 mmol) in dry benzene (0.5 mL) and AIBN (2 mg, 0.01 mmol) in benzene (0.5 mL) were added simultaneously over 12 h (syringe pump) to a refluxing solution of **193** (24 mg, 0.05 mmol) in dry benzene (1.5 mL). After the end of the addition, the mixture was refluxed for an arbitrary period of 4 h, cooled and evaporated. Flash chromatography of the residue over silica gel (10 x 120 mm) using 35% ethyl acetate--hexane gave **202a** and **202b** (5 mg, 28%) as an oil: FT-IR ($CHCl_3$ cast) 2260, 1792 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) (1:1 mixture of isomers) δ 0.09 (s), 0.10 (s), 0.17 (s), and 0.18 (s) [all signals together correspond to 6 H], 0.92 (s, 9 H), 2.42--2.92 (m, 4 H), 2.92--3.10 (m, 1 H), 4.20--4.55 (m, 3 or 4 H), 5.72 (s, 0.5 H), 5.73 (s, 0.5H), 5.99 (t, J = 3.0 Hz, 0.5 H), 6.12 (t, J = 2.4 Hz, 0.5 H); exact mass, *m/z* calcd for $C_{12}H_{16}NO_4Si$ $(M - C_4H_9)^+$ 266.0849, found 266.0847.

The use of triphenyltin hydride, higher temperature (refluxing toluene) or the use of triethylborane/air did not lead to any significant improvements. In one experiment, a small amount of *tert*-butyldimethylsilyloxy-3-hex-4-enenitrile **204** (19%) was isolated (see page XX).

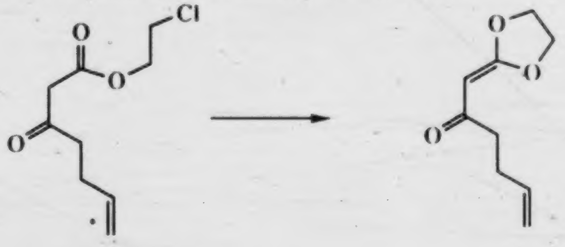
(2-Chloroethyl) 3-Oxo-6-heptenoate (234).



233 **234**

A solution of methyl-3-oxohept-6-enoate[54] (30.0 g, 0.436 mol) and titanium tetraisopropoxide (5 ml, 17 mmol) in 2-chloroethanol (750 mL) was stirred at 55 °C for 16 h and then at 75 °C for 24 h. The solvent was distilled off through a short Vigreux column under high vacuum (temperature < 70 °C) and the residue was partially purified by flash chromatography over silica gel (100 x 180 mm) using 10--20% ethyl acetate--hexane to afford impure **234** (40 g) as a reddish oil which was contaminated by some starting material and solvent. Removal of the solvent as above and Kugelrohr distillation of the residue (120--130 °C, 0.4 mm) gave **234** (26.0 g, 66%) as a colorless oil, contaminated by *ca* 10 mol% (by ^{1}H NMR) of some starting material: FT-IR ($CHCl_3$ cast) 1749, 1717, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.32--2.40 (m, 2 H), 2.68 (t, J = 7.2 Hz, 2 H), 3.52 (s, 2 H), 3.60 (t, J = 6.4 Hz, 2 H), 4.40 (t, J = 6.4 Hz, 2 H), 4.98--5.09 (dm, J = 10.4 Hz, 1 H), 5.03--5.09 (dm, J = 16.8 Hz, 1 H), 5.81 (ddt, J = 16.8 Hz, 10.4 Hz, 6.4 Hz, 1 H); exact mass, *m/z* calcd for $C_9H_{13}{}^{35}ClO_3$, 204.0553, found 204.0553.

1-(1,3-Dioxolan-2-ylidene)-5-hexen-2-one (235).[55]



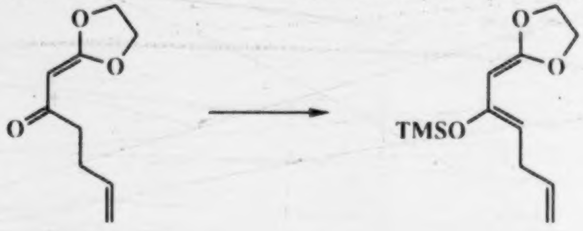
234 **235**

Dry # and powdered (325 mesh) potassium carbonate (Aldrich, 22.35 g) was added to a stirred solution of **234** (27.86 g, 0.136 mol) in dry DMF (105 mL). The mixture was stirred for 15 h and diluted with dry ether (350 mL, from a freshly opened can). The solids were allowed to settle and the solution was transferred under argon to a dry 1-L round-bottomed flask through a pad of Florisil#(120 x 35 mm).

# Potassium carbonate and Florisil were dried overnight at 80 °C under oil pump vacuum.

The same operation was repeated twice more with dry ether (2 x 150 mL) and the combined solvents were evaporated under water pump vacuum (protection from moisture). Kugelrohr distillation of the residue (85 °C, 0.01 mm) removed most of the DMF, leaving the crude ketene acetal **235** which was transferred (under argon) to a smaller flask. Kugelrohr distillation (105-135 °C, 0.01 mm) afforded **235** (19.88 g, 87%) as a colorless oil which solidifies when kept in a refrigerator: FT-IR ($CHCl_3$ cast) 1715, 1673, 1620, 1585, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.25--2.37 (m, 2 H), 2.42--2.52 (m, 2 H), 4.33--4.41 (m, 2 H), 4.51--4.62 (m, 2H), 4.88--5.05 (m, including s at δ 4.93, 3 H), 5.77 (ddt, J = 17.2, 10.1, 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 28.83, 41.45, 65.40, 68.16, 78.38, 114.41, 137.76, 168.32, 196.4; exact mass, *m/z* calcd for $C_9H_{12}O_3$ 168.0787, found 168.0785.

[1-(1,3-Dioxolan-2-ylidene)-2,5-hexadien-2-yl)oxy]trimethylsilane (218).



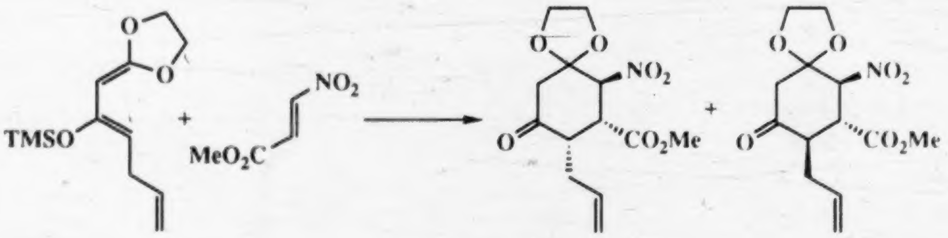
235 **218**

A solution of ketene acetal **235** (19.0 g, 113 mmol) in dry THF (100 mL) was added over 1 h to a cold (-78 °C) and stirred solution of lithium bis(dimethylphenylsilyl)amide [56,#] in dry THF (700 mL). The mixture was stirred for 10 min after the addition was complete and then chlorotrimethylsilane (18.46 g, 21.65 mL, 170 mmol) was added.

[#] Prepared by treatment of a cold (0 °C) and stirred solution of bis(dimethylphenylsilyl)amine[64] (39.33 g, 0.138 mol) in dry THF (700 mL) with *n*-butyllithium (1.6 M in hexanes, 78.8 mL, 0.126 mol) followed by stirring for 20 min at 0 °C

The cold bath was removed and the solution was allowed to warm to room temperature. The solvents were evaporated under water pump vacuum (protection from moisture). The residue was diluted with dry pentane (400 mL) and the solids were allowed to settle. The solution was transferred via cannula (under argon) to a dry 1-L round-bottomed flask through a pad of Florisil[##] (20 x 25 mm). Dilution with pentane (150 mL) and filtration through Florisil was repeated once more and the combined solvents were evaporated (protection from moisture). Kugelrohr distillation of the residue (115-125 °C, 0.12 mm) afforded **218** as a solution (*ca* 40% w/w) in bis(dimethyl)phenylsilylamine (65.82 g, *ca* 100%): FT-IR ($CHCl_3$ cast) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) (signals corresponding to **218** only) δ 2.8--2.92 (m, 2 H), 4.14--4.24 (m, 2 H), 4.28--4.40 (m, 2 H), 4.76 (t, J = 7.2 Hz, 1 H), 4.92--5.01 (dm, J = 10.0 Hz, 1 H), 5.07 (ddd, J = 17.2 , 3.9, 1.9 Hz, 1 H), 5.87 (ddt, J = 17.2, 10.0, 6.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ ; exact mass, *m/z* calcd for $C_{19}H_{22}O_2$ 282.1618, found 282.1620.

Methyl (6α,7β,8β)- and (6α,7β,8α)-6-Nitro-9-oxo-8-(2-propenyl)-1,4-dioxaspiro[4,5]decan-7-carboxylate (237a and 237b).



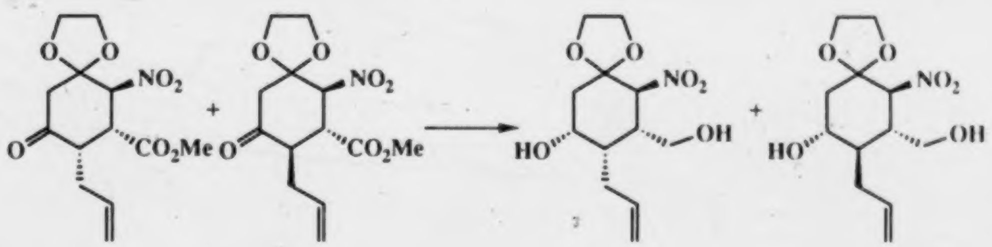
218 **219** **237a** **237b**

[##] Dried overnight at 80 °C under oil pump vaccuum

A solution of (Z)-methyl-3-nitropropenoate[65] (12.38 g, 94 mmol) in dry THF (15 mL plus 5 mL as a rinse) was added dropwise over 3 min to a cold (0 °C) and stirred solution of freshly prepared (1 hour old) diene **218** (*ca* 40% w/w in bis(dimethylphenylsilyl)amine; 65.82 g, *ca* 113 mmol) diluted with dry THF (10 mL). The mixture was stirred at 0 °C for 50 min and then aqueous hydrochloric acid 0.005 M (70 mL) in THF (300 mL) was added. The mixture was stirred for 1 h at 0 to 15°C and diluted with ether (1200 mL). The organic layer was separated and washed with water (3 x 100 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 x 20 cm) using 30--40% ethyl acetate--hexane afforded slightly impure material as a oil. This was allowed to crystallize and was then washed with a small amount of ether (in order to remove the liquid impurities present) to afford **237a** and **237b** (18.11 g, 64%) in a ratio of 83:17 [^{1}H NMR (400 MHz)] as a white solid. Carefull cristallization afforded pure **237a**, the mother liquor being enriched in **237b**. Compound **237a** had: FT-IR ($CHCl_3$ cast) 1732, 1559 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12--2.20 (m, 1 H), 2.33--2.42 (m, 1 H), 2.56 (d, J = 8.0 Hz, 1 H), 2.78 (d, J = 8.0 Hz, 1 H), 2.96--3.05 (m, 1 H), 3.70 (s, 3 H), 3.83 (dd, J = 10.0, 5.0 Hz, 1 H), 3.86--4.03 (m, 4 H), 5.00--5.05 (dm, J = 8.0 Hz, 2 H), 5.33 (d, J = 10.0 Hz, 1 H), 5.52--5.63 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 32.02, 44.46, 47.99, 48.66, 52.68, 65.76, 65.83, 85.04, 107.11, 118.11, 133.25, 169.60, 202.38; exact mass, *m/z* calcd for $C_{13}H_{17}NO_7$ 299.1005, found 299.1001. Anal. Calcd for $C_{13}H_{17}NO_7$: C, 52.14; H, 5.73, N, 4.68. Found: C, 52.04; H, 5.70, N, 4.64. The sample enriched in the minor isomer **237b** had: ^{1}H NMR ($CDCl_3$, 400 MHz) (most significant signals only) δ 3.55 (dd, J = 10.4, 9.6 Hz, 1 H), 3.71 (s, 3 H), 5.05--5.10 (dm, 12.0 Hz, 2 H), 5.30 (d, J = 10.0 Hz, 1 H), 5.65--5.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 30.81, 46.14, 49.09, 50.42, 52.90, 65.88, 88.42, 106.93, 118.33, 133.78, 171.16, 200.88.

When the same reaction was performed under similar conditions using (Z)-3-nitropropenoate (317 mg, 2.42 mmol) and diene **218** (*ca* 40% w/w in disilylamine; *ca* 3.39 mmol), the yield of **237a** and **237b** was increased (606 mg, 84%). When the reaction was done at -10 °C, the ratio of isomers **237a** vs **237b** increased to 89:11 but the yield was similar.

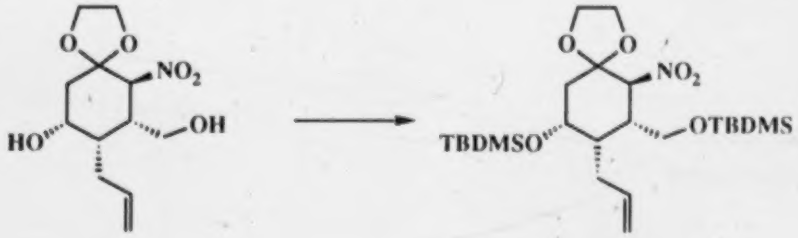
(7α,8α,9α,10β)- and (7α,8β,9α,10β)-9-(Hydroxymethyl)-10-nitro-8-(2-propenyl)-1,4-di-oxaspiro[4,5]decan-7-ol (238a and 238b).



237a **237b** **238a** **238b**

A solution of **237a** and **237b** (83:17, 308 mg, 1.03 mmol) in 2:1 toluene--dichloromethane (26 mL) was added dropwise over 1 min to a cold (-10 °C) and stirred solution of diisobutylaluminum hydride (1 M in dichloromethane, 4.5 mL, 4.5 mmol) in dry dichloromethane (20 mL). The mixture was stirred at -10 °C for 15 min and then quenched by careful addition of methanol (1 mL). The cooling bath was removed, and Celite and of sodium sulfate decahydrate were added in one portion. The resulting suspension was stirred vigorously for 15 min and then the solids were filtered off through a short pad (40 x 60 mm) of Celite and washed with dichloromethane. The combined solvents were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (25 x 150 mm) using 40--60% ethyl acetate--hexane afforded **238b** (78 mg, 28 %) and the chromatographically less mobile **238a** (149 mg, 53 %), both as white solids#. The chromatographically more mobile **238b** had: FT-IR ($CHCl_3$ cast) 3640--3100, 1561 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88--2.14 (m, 3 H), 2.21--2.47 (m, 2 H), 2.60 (broad t, J = 4.0 Hz, 1 H), 2.82--3.0 (m, 1 H), 3.60--3.82 (m, 2 H), 3.85--4.10 (m, 5 H), 4.83 (d, J = 9.2 Hz, 1 H), 5.0--5.15 (m, 2 H), 5.68--5.86 (m, 1 H); mass for $C_{12}H_{19}NO_6$ for $C_{12}H_{19}NO_6$ (chemical ionisation) 291 $(M + 18)^+$. The chromatographically less mobile **238a** had: FT-IR ($CHCl_3$ cast) 3600--3100, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91--2.05 (m, 2 H), 2.17--2.29 (m, 1 H), 2.32--2.52 (m, 3 H), 2.53--2.65 (m, 2 H), 3.78--3.88 (broad s, 2 H), 3.96--4.12 (m, 5 H), 4.95 (dd, J = 4.4, 1.0 Hz, 1 H), 5.19 (dm, J = 10.0 Hz, 1 H), 5.17 (dm, J = 16 Hz,1 H), 5.79--5.90 (m, 1 H); mass for $C_{12}H_{19}NO_6$ (chemical ionisation) 291 $(M + 18)^+$.

(7α,8α,9α,10β)-Dimethyl(1,1-dimethylethyl)-[[9-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-10-nitro-8-(2-propenyl)-1,4-dioxaspiro[4,5]decan-7-yl]oxy]silane (239).



238a **239**

Imidazole (814 mg, 11.97 mmol) and then *tert*-butylchlorodimethylsilane (818 mg, 5.42 mmol) were added to a stirred solution of **238a** (369 mg, 1.36 mmol) in dry DMF (6 mL). The mixture was

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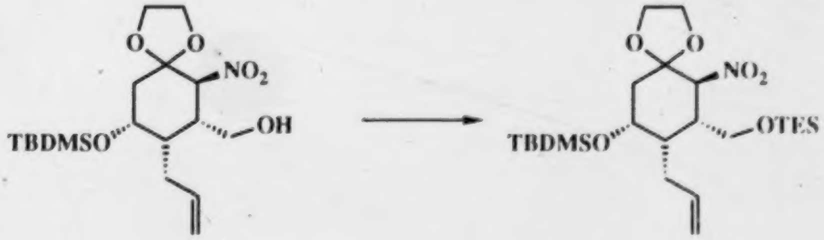
# The yield is very dependent on the temperature of the reaction and on the order of addition of the reactants.

stirred at 50 °C overnight, poured into ether (60 mL), and washed with saturated aqueous sodium bicarbonate (10 mL). The organic layer was washed with water (10 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (40 x 180 mm) using 4--6% ethyl acetate--hexane afforded **239** (619 mg, 91%) as a thick oil: With the exception of the signals attribuablee to the silicon substituents, the ^{1}H NMR spectra of **239** and **250** (from following experiment) are identical.

(7α,8α,9α,10β)-Dimethyl(1,1-dimethylethyl)-[[9-[[[triethylsilyl]oxy]-methyl]-10-nitro-8-(2-propenyl)-1,4-dioxaspiro[4,5]decan-7-yl]oxy]silane (250).

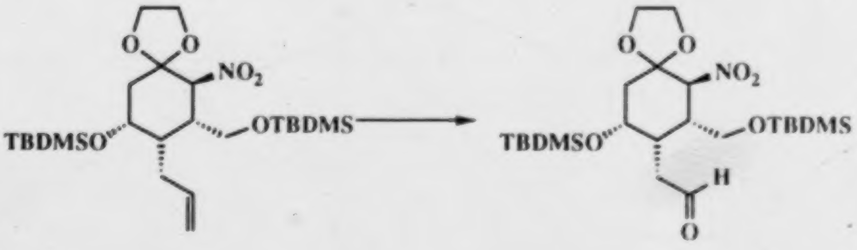


261 **250**

Chlorotriethylsilane (0.852g, 0.950 mL, 5.66 mmol) and DMAP (a few crystals) were added in one portion to a stirred solution of **261** (1.90 g, 4.92 mmol) and triethylamine (0.746 g, 1.03 mL, 7.38 mmol) in dry dichloromethane (16 mL). Stirring was continued for 3 h at room temperature and the mixture was processed as described for **266**. Flash chromatography of the residue on silica gel (50 x 180 mm) using 4--6% ethyl acetate--hexane afforded **250** (2.42 g, 98%) as a thick oil: FT-IR ($CHCl_3$ cast) 1552 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 6 H) and 0.07 (s, 6 H), 0.57 (q, J = 8.0 Hz, 6 H), 0.84--1.0 (m, 18 H), 1.83 (dd, J = 14.3, 8.0 Hz, 1 H), 1.98--2.39 (m, 4 or 5

H), 2.46--2.61 (m, 1 H), 3.68 (dd, J = 10.0, 5.5 Hz, 1 H), 3.74--3.88 (m, 1 H), 3.90--4.09 (m, 6 H), 4.88 (d, J = 8.0 Hz, 1 H), 4.91--5.12 (m, 2 H), 5.72--5.98 (m, 1 H); ^{13}C NMR ($CDCl_3$, 106.6 MHz) δ -4.93, -4.57, 4.28, 6.73, 18.05, 25.77, 39.98, 42.68, 60.40, 64.93, 65.18, 69.41, 86.42, 106.85, 115.44, 138.26; exact mass, *m/z* calcd for $C_{24}H_{47}NO_6Si_2$ 501.2942, found 501.2940. Anal. Calcd for $C_{24}H_{47}NO_6Si_2$: C, 57.42; H, 9.44; N, 2.79. Found: C, 57.49; H, 9.29; N, 2.69.

(7α,8α,9α,10β)-7-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-9-[[[dimethyl-(1,1-dimethylethyl)silyl]oxy]methyl]-10-nitro-1,4-dioxaspiro[4,5]decan-8-yl]ethanal (243).

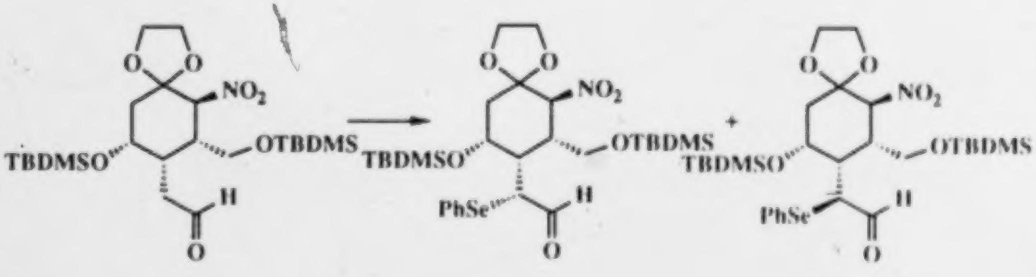


239 **243**

(a) (7α,8α,9α,10β)-3-[7-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-9-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-10-nitro-1,4-dioxaspiro[4,5]decan-8-yl]propane-1,2-diol (241). Osmium tetroxide (2.5% w/v in *tert*-butanol, 4 mL, 0.3 mmol) was added to a stirred solution of **239** (3.0 g, 5.98 mmol) in acetone (30 mL) and water (12 mL). Stirring was continued for 15 min and then (*N*)-methylmorpholine-(*N*)-oxide monohydrate (970 mg, 7.2 mmol) was added in one portion. The mixture was stirred at room temperature for 6 h and diluted with ether (250 mL). The organic layer was washed with water (1 x 20 mL), 10% w/v aqueous sodium bisulfate (2 x 15 mL), and water (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (60 x 180 mm) using 50% ethyl acetate--hexane gave **242** (3.10 g, 96%) as a colorless oil.

(b) (7α,8α,9α,10β)-7-[[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-9-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-10-nitro-1,4-dioxaspiro[4,5]decan-8-yl]ethanal (243). Sodium periodate (186 mg, 0.873 mmol) was added in one portion to a stirred solution of **242** (360 mg, 0.67 mmol) in methanol (8 mL). The suspension was stirred at room temperature for 2 h and the mixture was diluted with ether (60 mL), and washed with water (2 x 10 mL), and the organic layer was dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (60 x 180 mm) using 30% ethyl acetate--hexane gave **243** (290 mg, 85%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ -0.02--0.12 [four s, 6 H], 0.85 (s, 9 H), 1.69 (dd, J = 13.5, 12.0 Hz, 1 H), 1.84 (ddd, J = 13.5, 4.5, 1.0 Hz, 1 H), 2.58--2.73 (m, 3 H), 2.96 (broad quintet, J = 5.5 Hz, 1 H), 3.64 (d, J = 4.1 Hz, 2 H), 3.84--4.12 [m, including a dt (J = 11.5, 4.8 Hz) at δ 4.06, 5 H], 4.75 (d, J = 12.0 Hz, 1 H), 9.74 (broad s, 1 H).

(7α,8α,9α,10β)-[7-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-9-[[[dimethyl(1,1-dimethylethyl)silyl]oxy]methyl]-10-nitro-1,4-dioxaspiro[4,5]decan-8-yl]-(phenylseleno)ethanal (245a and 245b).



243 **245a** **245b**

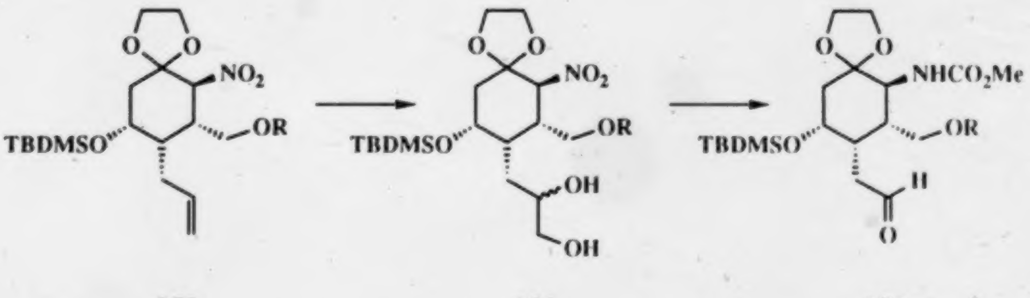
Triethylamine (0.279 mL, 2 mmol), chlorotrimethylsilane (0.202 mL, 1.6

mmol) and then dry zinc chloride (*ca* 10 mg) were added to a stirred solution of **243** (100 mg, 0.2 mmol) in dry toluene (3 mL). The mixture was stirred at 80 °C for 4 h, allowed to cool to room temperature, and then cooled to -20 °C. Benzeneselenyl chloride (305 mg, 1.6 mmol) in dry dichloromethane (2 mL) was added over 30 sec to the resulting cold and stirred mixture of silylenolethers. The cooling bath was removed and the mixture was allowed to reach room temperature. The mixture was diluted with dichloromethane (25 mL) and washed with saturated aqueous sodium bicarbonate (2 x 5 mL) and water (5 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 180 mm) using 30% ethyl acetate--hexane gave **245a** and **245b** (120 mg, 92 %) in a ratio [^1H NMR (200 MHz)] of 4:1. Compound **245a** had: ^1H NMR ($CDCl_3$, 200 MHz) (most characteristic signals of the major compound only) δ 5.30 (broad s, 1 H), 9.52 (d, J = 3.0 Hz, 1 H).

In a different run, the *Z/E* mixture of silyl enol ethers **244a** and **244b** (8:1 ratio) was isolated (saturated aqueous sodium bicarbonate work-up) and a small amount of pure (Z)-silylenolether **244a** could be recovered after flash chromatography. Treatment of this material with PhSeCl as above gave **245a** and **245b** in a 1:8 ratio [^1H NMR (200 MHz)] respectively, leading to the conclusion that the (Z) enolether **244a** affords mainly **245b** whereas the (*E*)-enol ether **244b** gives mainly **245a**...The (*Z*)-enol ether **244a** had: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87 (s) and 0.88 (s) [both signals together correspond to 18 H], 1.85 (d, J = 4.0 Hz, 2 H), 2.57--2.73 (m, 1 H), 3.37--3.49 (m, 1 H), 3.55 (dd, J = 10.4, 6.0 Hz, 1 H), 3.85--4.10 (m, 5 H), 4.35 (dd, J = 11.0, 6.0 Hz, 1 H), 4.73 (d, J = 11.5 Hz, 1 H), 6.40 (d, J = 6.5 Hz, 1 H). The (*E*)-enol ether **244b** had: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 18 H), 1.75--1.88 (m, 2 H), 2.52--2.80 (m, 2 H), 3.41 (dd, J = 9.6, 9.2 Hz, 1 H), 3.81--4.08 (m, 5 H), 4.59 (d, J = 12.0 Hz, 1 H), 4.81 (dd, J =

11.2, 11.0 Hz, 1 H), 6.28 (d, J = 12.0 Hz, 1 H). The seleno aldehyde **245b** had: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.00--0.25 [4 x (s), 12 H], 0.89 (s, 9 H), 0.97 (s, 9 H), 2.10--2.95 (m, 4 H), 3.68 (dd, J = 11.2, 4.8 Hz, 1 H), 3.85--4.39 (m, 6 H), 4.65--4.79 (m, 1 H), 5.09 (broad d, J = 3.2 Hz, 1 H), 7.27--7.75 (m, 5 H), 9.40 (d, J = 4.8 Hz, 1 H).

Methyl (6α,7β,8β,9β)-[9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7-[[[triethylsilyl]oxy]-methyl]-8-(2-oxoethyl)-1,4-dioxaspiro[4,5]decan-6-yl]carbamate (253).



250 251 253

(a) (7α,8α,9α,10β)-3-[7-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-9-[[[triethylsilyl]oxy]methyl]-10-nitro-1,4-dioxaspiro[4,5]decan-8-yl]propane-1,2-diol (251). The diol **251** (R = Et_3Si) was prepared in 95% yield using osmium tetroxide and *N*-methylmorpholine-*N*-oxide in aqueous acetone as described for the conversion of **239** to **242**.

(b) Methyl (6α,7β,8β,9β)-[9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7-[[[triethylsilyl]oxy]-methyl]-8-(2,3-dihydropropyl)-1,4-dioxaspiro[4,5]decan-6-yl]carbamate (252). Treatment of **251** (R = Et_3Si) (382 mg, 0.71 mmol) in 2:1

ethanol--methanol (12 mL) with Raney Nickel[#] (grade T-1[66], *ca* 1.46 g) as --described for the conversion of **266** to **267**, gave the corresponding crude amine (300 mg). This amine was dissolved in dry dichloromethane (10 mL) and the solution was cooled to -45 °C. Triethylamine (0.172 mL, 1.20 mmol) and methyl chloroformate (68 µL, 0.87 mmol) were added to this cold and stirred solution. The mixture was stirred at -45 to -20 °C for 15 min and was then quenched by addition of saturated aqueous sodium bicarbonate (1 x 5 mL). The mixture was diluted with ether (30 mL) and the organic layer was washed with water (1 x 5 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 180 mm) using 70% ethyl acetate--hexane gave **252** (R = Et_3Si) (176 mg, 44% from **251**) as a colorless oil.

(c) Methyl (6α,7β,8β,9β)-[9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7-[[[triethylsilyl]oxy]-methyl]-8-(2-oxoethyl)-1,4-dioxaspiro[4,5]decan-6-yl]-carbamate (253). Treatment of **252** (R = Et_3Si) (44 mg, 0.078 mmol) with sodium periodate (45 mg, 0.21 mmol) as described for the conversion of **242** to **243** gave **253** (R = Et_3Si) (27 mg, 65%)[##]: ^1H NMR ($CDCl_3$, 200 MHz) [The signals are either broadened or doubled due to the presence of rotational isomers (see discussion)] δ 0.05 (s) and 0.07 (s) [both signals together correspond to 6 H], 0.55 (q, J = 8.0 Hz, 6 H), 0.83 (s, 9 H), 0.92 (t, J = 8.0 Hz, 9 H), 1.55--1.95 (m, 4 H), 2.35 (broad dd, J = 16.0, 4.8 Hz, 1 H), 2.58 (ddd, J = 16.0, 7.0, 2.5 Hz, 1 H), 2.80--2.95 (m, 1 H), 3.52 (dd, J = 10.2, 8.8 Hz, 1 H), 3.58--3.79 (m, -----

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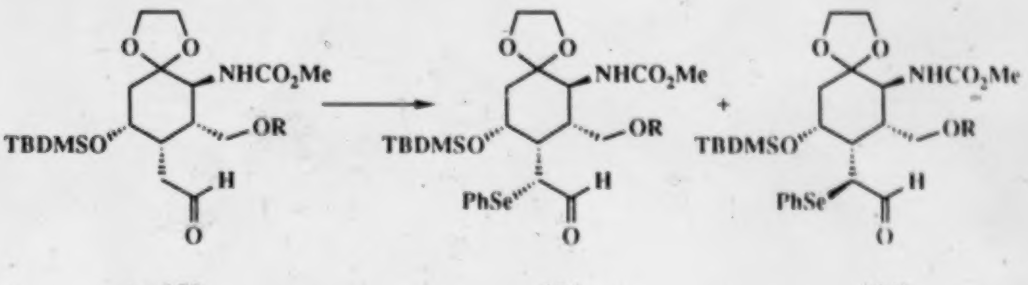
[#] The procedure for the preparation of the Raney Nickel described by Dominguez *et al.*[66] was followed, but with some important modifications. Care was taken to remove all traces of base on the catalyst by washing it thoroughly with water (3 times), 0.005 M aqueous acetic acid (3 times), water (3 times or until pH = 7), and absolute ethanol (5 times). The catalyst was kept under ethanol at 0 °C.

[##] The corresponding bis(*tert*-butyldimethylsilyl) derivative **253** (R = *t*-$BuMe_2Si$) was obtained from **250** (R = *t*-$BuMe_2Si$) in similar yield (40% overall) using the same procedure.

including s at δ 3.65, 4 H), 3.80--4.11 (m, 5 H), 4.40 (broad d, J = 10.0 Hz, 0.25 H) and 4.60 (broad d, J = 10.0 Hz, 0.75 H), 9.65 (broad s, 1 H).

Methyl (6α,7β,8β,9β)-[9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7-[[[triethylsilyl]oxy]methyl]-8-[2-oxo-1-(phenylseleno)ethyl]-1,4-dioxaspiro[4,5]decan-6-yl]carbamate (254a and 254b)

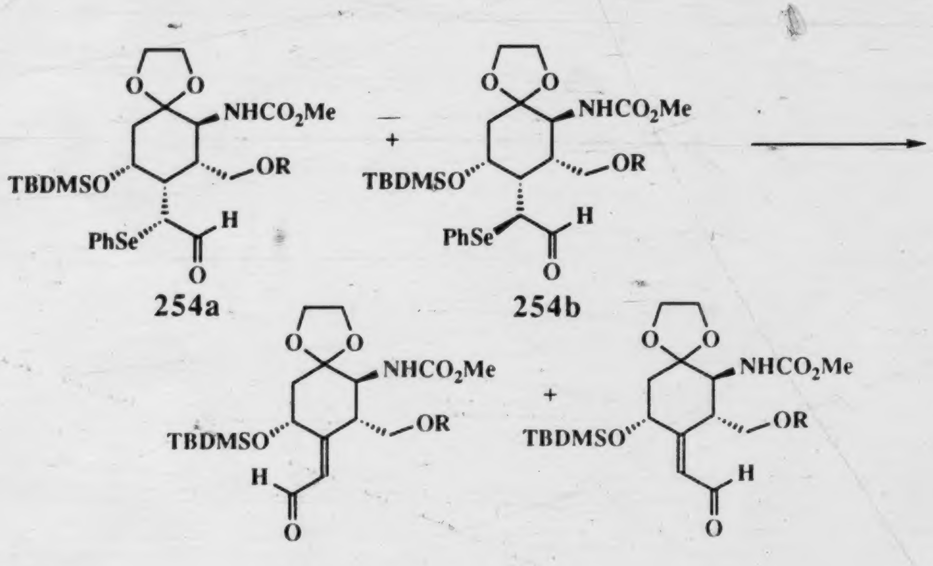


253 **254a** **254b**

Treatment of **253** (R = Et$_3$Si) with triethyl-amine/chlorotrimethylsilane and benzeneselenyl chloride as described for the conversion of **243** to **245a** and **245b** (70%) gave **254a** and **254b** (R = Et$_3$Si) in a ratio [^{1}H NMR (200 MHz)] of 3:1: ^{1}H NMR (CDCl$_3$, 200 MHz) (Most characteristic peaks only) δ 9.17 (broad d, J = 8.0 Hz, 0.25 H), 9.25--9.40 (broad s, 0.75 H).

Using the same procedure, **254a** and **254b** (R = *t*-BuMe$_2$Si) were obtained from **253** (R = *t*-BuMe$_2$Si) in similar yield but the ratio of isomers was 5.3:1 instead of 3:1. ^{1}H NMR (CDCl$_3$, 200 MHz) (most characteristic peaks only) δ 9.18 (broad d, J = 8.4 Hz, 0.16 H), 9.25--9.40 (broad s, 0.86 H).

Methyl (*Z*)- and (*E*)-(6α,7β,9β)-[9-[[Dimethyl(1,1-dimethylethyl)silyl]-oxy]-7-[[[triethylsilyl]oxy]-methyl]-8-(2-oxoethylidene)-1,4-dioxaspiro[4,5]decan-6-yl]carbamate (255a and 255b).



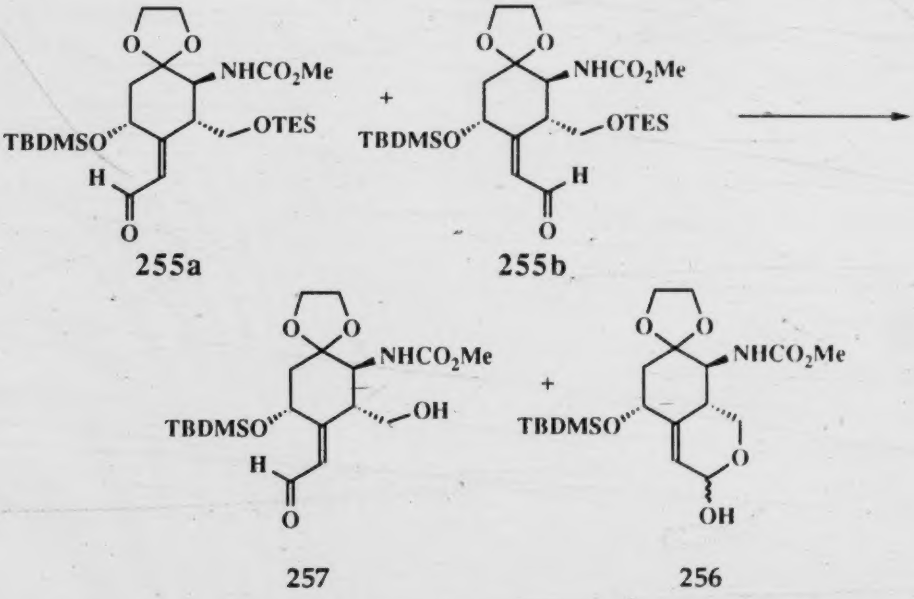
255a **255b**

Pyridine (26 µl, 0.33 mmol) and 30% aqueous hydrogen peroxide (18 µl, 0.17 mmol) were added to a stirred solution of **254a** and **254b** (R = Et$_3$Si) (3:1, 19 mg, 0.028 mmol) in dichloromethane (1 mL) and THF (0.2 mL). The mixture was stirred at room temperature for 16 h and then diluted with dichloromethane (10 mL). The resulting mixture was washed with saturated aqueous sodium bicarbonate (1 x 3 mL), 10% aqueous copper sulfate (1 x 3 mL), 10% w/v aqueous sodium bisulfite (1 x 3 mL), and water (1 x 3 mL), and dried (MgSO$_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 x 150 mm) using 30% ethyl acetate--hexane gave **255a** and **255b** (R = Et$_3$Si) (5.5 mg, 37%) as a 2.1:1 mixture of isomers: ^{1}H NMR (CDCl$_3$, 400 MHz) (most characteristic signals only) δ 4.35--4.40 (m, *ca* 0.3 H), 4.71--4.82 (m, *ca* 0.7 H), 5.95 (d, J = 8.0 Hz, 1 H), 9.90 (d, J = 8.0 Hz, 0.3 H), 10.55

(broad d, J = 8.0 Hz, 0.7 H).

Using the same procedure, **255a** and **255b** (R = *t*-BuMe$_2$Si) were obtained from **254a** and **254b** (R = *t*-BuMe$_2$Si) in similar yield but the ratio of isomers was 5.3:1 instead of 3:1.

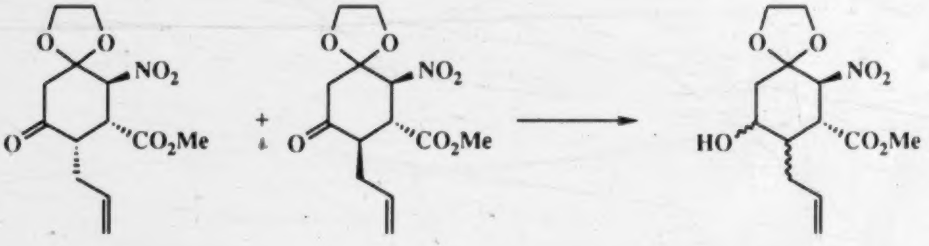
Methyl (Z)-(6α,7β,9β)-[9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7-(hydroxymethyl)-8-(2-oxoethylidene)-1,4-dioxaspiro[4,5]decan-6-yl]carbamate (257) and Methyl (5α,8β,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)-3,5,6,7,8,8a-hexahydro-3-hydroxy-1*H*-2-benzopyran-8-yl)carbamate (256).



Trifluoroacetic acid (2.1 μl, 0.028 mmol) was added to a cold (0 °C) and stirred solution of **255a** and **255b** (7:3, 5.0 mg, 0.0094 mmol) in 3:1 THF--water (0.65 mL). The mixture was stirred at 0 °C for 1 h and diluted with dichloromethane (10 mL). The mixture was washed with saturated aqueous sodium bicarbonate (2 mL), and water (2 mL), and dried (MgSO$_4$).

Evaporation of the solvent and flash chromatography of the residue over silica gel (5 x 60 mm) using 75% ethyl acetate--hexane gave **257** and **256** in a 7:3 (^{1}H NMR) ratio. Compound **257** had: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93 (dd, J = 13.0, 11.0 Hz, 0.71 H), 2.22 (dd, J = 13.0, 5.0 Hz, 0.71 H), 4.60 (dd. J = 11.6, 5.0 Hz, 0.71 H), 6.3 (d, J = 7.2 Hz, 0.71 H), 10.69 (d, J = 7.2 Hz, 0.71 H). No other signals for an aldehyde were present; instead signals corresponding to the presumed lactol(s) **256** were observed. Compound(s) **256** had ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.68--4.75 (m, 0.29 H), 5.38--5.47 (m, 0.29 H), 5.90--5.95 (m, 0.29 H).

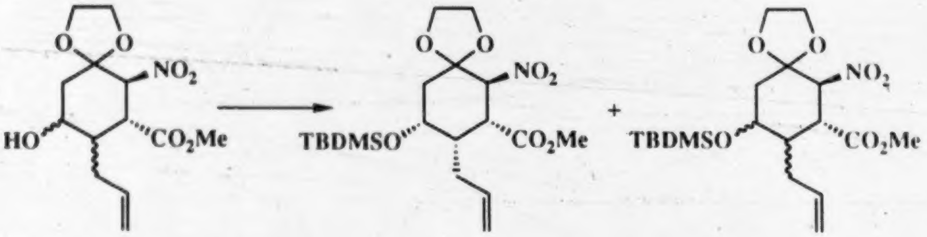
Methyl (6α,7β)-[9-Hydroxy-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4,5]decan-7-yl]carboxylate (259).



237a **237b** **259**

Sodium borohydride (6.0 g, 157.0 mmol) was added in one portion to a cold (-78 °C) and stirred solution of **237a** and **237b** (83:17, 9.02 g, 30.2 mmol) in 1:5 dichloromethane--methanol. The mixture was allowed to reach room temperature over 2 h, and was then quenched by addition of saturated aqueous ammonium chloride (30 mL) Most of the solvents were evaporated and the residue was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with water (50 mL), and brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residual oil over silica gel (50 x 200 mm) using 50--60% ethyl acetate--hexane afforded **259** as a mixture of three isomeric alcohols (8.78 g, 97%).

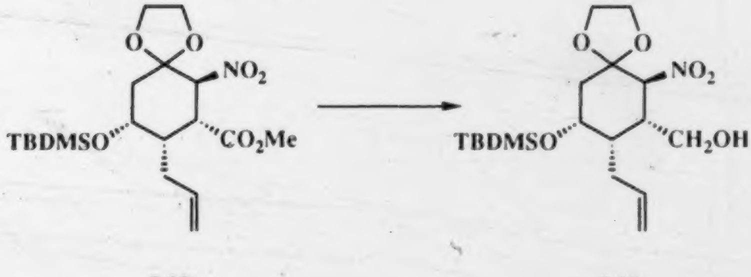
Methyl (6α,7β,8α,9α)-[9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4,5]decan-7-yl]carboxylate (260).



259 **260** **260'**

Dry lutidine (6.17 g, 6.7 mL, 57.67 mmol) was injected into a stirred solution of **259** (8.68 g, 28.83 mmol) in dry dichloromethane (50 mL) kept at room temperature by a water bath. Immediatly thereafter, *tert*-butyldimethylsilyl triflate (11.43g, 9.94 mL, 43.24 mmol) was injected, the bath was removed, and the mixture was stirred for 1 h. The mixture was diluted with ether (250 mL) and washed (slow addition at first) with 10% w/v aqueous copper sulfate (75 mL). The aqueous layer was extracted with ether (250 mL) and the combined extracts were washed with 10% w/v aqueous copper sulfate (75 mL), water (75 mL), and brine (75 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (120 x 180 mm) using 5--10% ethyl acetate--hexane gave **260** (7.5 g, 63%) and a 1:1 mixture of 2 isomeric silyl ethers **260'** (3.05g, 25%). Coumpound **260** had: FT-IR ($CHCl_3$ cast) 1740, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 6 H), 0.89 (s, 9 H), 1.77 (d, J = 8.2 Hz) and 1.85 (dt, J = 14.5, 8.0 Hz) [both signals together correspond to 3 H], 2.37--2.48 (m, 1 H), 2.50--2.65 (dm, J = 14.5 Hz, 1 H), 3.52 (dd, J = 12.0, 4.5 Hz, 1 H), 3.62 (s, 3 H), 3.87--4.14 [m, including a dt (J = 8.0, 5.0 Hz) at δ 4.06, 5 H], 4.87--5.00 [m, including d (J = 12.0 Hz) at δ 4.97, 3 H], 5.49--5.71 (m, 1 H); ^{13}C NMR (CDCl$_3$, 106.6 MHz) δ -4.75, -4.78, 18.04, 25.74, 27.11, 40.48, 42.66, 45.01, 51.99, 65.34, 65.59, 68.83, 84.87, 107.57, 115.90, 137.12, 170.76; exact mass, *m/z* calcd for $C_{19}H_{33}NO_7Si$ 415.2027, found 415.2040.

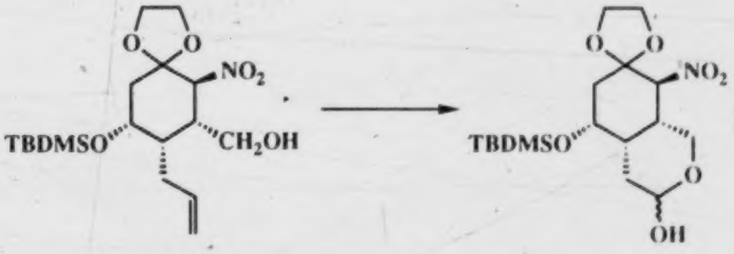
(6α,7β,8β,9β)-[9-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-6-nitro-8-(2-propenyl)-1,4-dioxaspiro[4,5]decan-7-yl]methanol (261).



260 **261**

A solution of **260** (2.78 g, 6.68 mmol) in dry dichloromethane (30 mL + 5 mL as a rinse) was added by cannula over 4 min to a cold (-30 °C) and stirred solution of diisobutylaluminium hydride (1 M in dichloromethane, 20 mL, 20 mmol) in dry dichloromethane (140 mL). The mixture was stirred for 15 min and quenched by careful addition of methanol (10 mL). The bath was removed and a large amount of Celite and sodium sulfate decahydrate (*ca* 50 g) were added. The mixture was then stirred for 15 min and the solids were filtered off through a pad of Celite (70 x 90 mm) and washed with dichloromethane. The solvent was dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (25 x 180 mm) using 20% ethyl acetate--hexane afforded **261** (2.27 g, 87%) as a thick, colorless oil: FT-IR (CHCl$_3$ cast) 3650-3100, 1640, 1553 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.07 (s, 6 H), 1.70--1.86 (m, 2 H), 1.92--2.16 (m, 2 H), 2.25--2.39 (m, 1 H), 2.40--2.56 (m, 1 H), 2.63 (s, J = 5.3 Hz, 1 H), 3.64--3.80 (m, 2 H), 3.95 (s, 4 H), 4.04 (dt, J = 8.7, 3.8 Hz, 1 H), 4.82 (d, J = 9.5 Hz, 1 H), 5.02--5.20 (m, 2 H), 5.75--6.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -4.89, -4.63, 17.99, 25.72, 40.37, 42.01, 60.09, 65.16, 65.82, 69.09, 86.68, 107.09, 115.91, 138.65; exact mass, *m/z* calcd for $C_{18}H_{33}NO_6Si$ 387.2077, found 387.2074. Anal. Calcd for $C_{18}H_{33}NO_6Si$: C, 55.78; H, 8.58; N, 3.61. Found: C, 56.12; H, 8.76; N, 3.79.

(4aα,5β,8α,8aα)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-hydroxy-8-nitro-1*H*-2-benzopyran (262a and 262b).

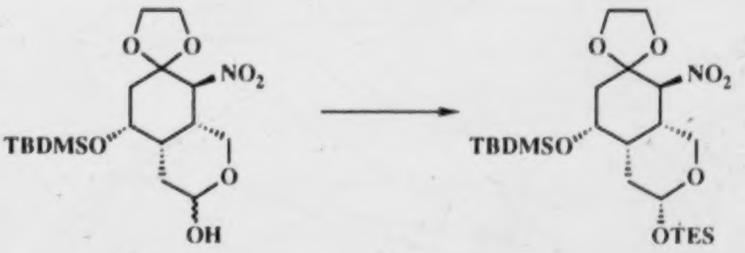


261 **262a** and **262b**

Osmium tetroxide (2.5% w/v in *tert*-butanol, 4 mL) was added to a stirred solution of **261** (2.13 g, 5.5 mmol) in 2:2:1 carbon tetrachloride--water--*tert*-butanol (75 mL). The mixture was stirred for 15 min, and sodium periodate (2.93 g, 13.75 mmol) was added in one portion. After 3 h, the resulting suspension was diluted with water (20 mL) and extracted with ether (400 mL). The organic layer was washed with water (20 mL), 10% w/v aqueous sodium bisulfite (20 mL), and water (20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (60 x 180 mm) using 25--30% ethyl acetate--hexane gave **262a** and **262b** (2.10g, 98%) as a white solid consisting of a 3:1 mixture [^{1}H NMR (400 MHz)] of isomeric lactols: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.04 (s) and 0.07 (s) [both signals together correspond to 6

H], 0.84 (s, 9 H), 1.16--1.38 (m, 0.25 H), 1.43--1.60 (m, 0.75 H), 1.72--1.85 (m, 2.7 H), 1.93--2.05 (m, 0.25 H), 2.18--2.35 (m, 0.25 H), 2.40--2.70 (m, 2.5 H), 3.20--3.30 (m, 0.75 H), 3.55--3.75 (m, 0.5 H), 3.85--4.02 (m, 4 H), 4.02--4.21 (m, 2 H), 4.67--4.78 (m, 0.25 H), 5.03 (d, J = 12.5 Hz) and 5.05 (d, J = 12.5 Hz) [both signals together correspond to 1 H), 5.40 (broad s, 0.75 H).

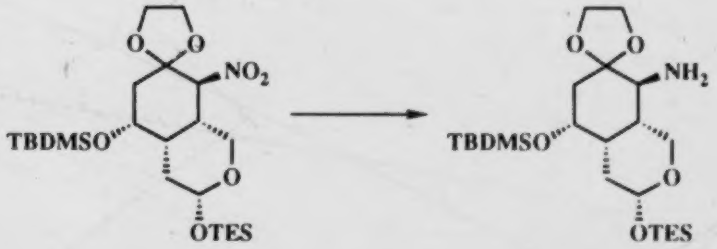
(3α,4aβ,5α,8β,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-8-nitro-3-[[triethylsilyl]oxy]-1*H*-2-benzopyran (266).



262a and 262b **266**

Triethylamine (587 mg, 0.81 mL, 5.80 mmol), chlorotriethylsilane (700 mg, 0.78 mL, 4.66 mmol) and then *N,N*-(dimethylamino)pyridine (*ca* 100 mg) were added to a cold (0 °C) and stirred solution of **262a** and **262b** (1.51 g, 3.87 mmol) in dry dichloromethane (28 mL). The cold bath was removed and the mixture was stirred for 3 h. It was then diluted with ether (200 mL), washed with saturated aqueous sodium bicarbonate (30 mL), and 1:1 water--brine (30 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (25 x 180 mm) using 6--8% ethyl acetate--hexane afforded **266** as a single isomer (1.88g, 96%) as a waxy solid: FT-IR ($CHCl_3$ cast) 1553, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.06 (s, 6 H), 0.52--0.69 (m, 6 H), 0.85--1.00 (m including s at δ 0.89, 18 H), 1.26--1.43 (m, 1 H), 1.73--1.92 (m, 3 H), 2.23 (dq, J = 12.4 Hz, 4.8 Hz, 1 H), 2.37--2.50 (dm, J = 12.2 Hz, 1 H), 3.53 (dd, J = 13.0, 2.2 Hz, 1 H), 3.67 (d, J = 13.0 Hz, 1 H), 3.83--4.01 (m, 4 H), 4.02--4.16 (m, 1 H), 4.67 (dd, J = 9.0, 2.2 Hz, 1 H), 5.06 (d, J = 12.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -4.91, 4.82, 6.59, 17.87, 34.76, 39.22, 39.59, 65.02, 65.48, 65.69, 67.93, 85.52, 97.63, 108.08; exact mass, *m*/*z* calcd for $C_{23}H_{44}NO_7Si_2$ 502.2656, found 502.2670. Anal. Calcd for $C_{23}H_{44}NO_7Si_2$: C, 54.81; H,.9.01; N, 2.78. Found: C, 54.95; H, 8.90; N, 2.98.

(3α,4aβ,5α,8β,8aβ)-8-Amino-5-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-[[triethylsilyl]oxy]-1*H*-2-benzopyran (267).



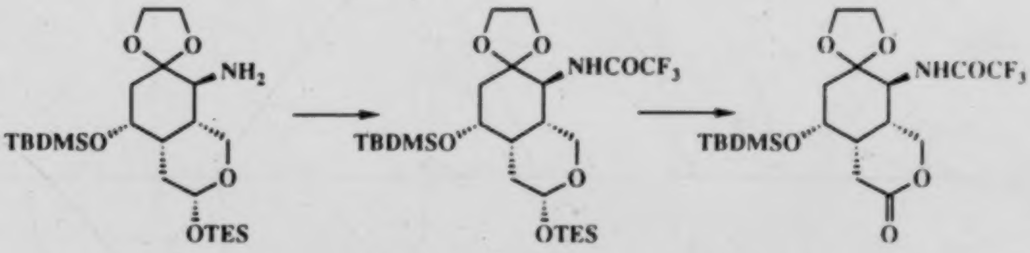
266 **267**

A solution of **266** (1.85 g, 3.67 mmol) in ethyl acetate (4 mL + 1 mL as a rinse) was added to a suspension of Raney Nickel (grade T-1, *ca* 4.5 g)[66,#] in 2:1 ethanol--methanol (70 mL) contained in a thick-wall 500-mL pyrex bottle. The mixture was shaken for 16 h on a Parr hydrogenator under hydrogen at 50 psi. The solvent was transferred by cannula (under argon) to a 500-mL round-bottomed flask through a pad of Celite (25 x 40 mm) and the catalyst was washed with ethyl acetate (40 ml) and dichloromethane (30 mL).

[#] The procedure for the preparation of the Raney Nickel described by Dominguez *et al.*[66] was followed, but with some important modifications. Care was taken to remove all traces of base on the catalyst by washing it thoroughly with water (3 times), 0.005 M aqueous acetic acid (3 times), water (3 times or until pH = 7), and absolute ethanol (5 times). The catalyst was kept under ethanol at 0 °C.

Evaporation of the combined solvents and flash chromatography of the residue over silica gel (20 x 60 mm) using first 50% ethyl acetate--hexane and then ethyl acetate gave **267** (1.55 g, 89%) as a waxy white solid: FT-IR ($\mathrm{CHCl_3}$ cast) 3347 $\mathrm{cm^{-1}}$; ^{1}H NMR ($\mathrm{CDCl_3}$, 400 MHz) δ 0.03 (s, 6 H), 0.62 (q, J = 8.0 Hz, 6 H), 0.85 (s, 9 H), 0.95 (t, J = 8.0 Hz, 9 H), 1.0--1.18 (broad, ~ 2 H), 1.26 (broad d, J = 12.0 Hz, 1 H), 1.43 (dt, J = 14.0, 9.6 Hz, 1 H), 1.64 (t, J = 13.4 Hz, 1 H), 1.76--1.83 (dm, J = 13.6 Hz, 2 H), 2.06 (ddd, J = 13.6, 8.4, 4.0 Hz, 1 H), 3.08 (d, J = 11.6 Hz, 1 H), 3.41 (dd, J = 12.0, 2.2 Hz, 1 H), 3.94 (dt, J = 12.0, 5.0 Hz, 1 H), 3.98 (s, 4 H), 4.39 (d, J = 11.8 Hz, 1 H), 4.66 (broad d, J = 8.4 Hz, 1 H); ^{13}C NMR ($\mathrm{CDCl_3}$, 100.6 MHz) δ -4.80, 4.96, 6.73, 18.07, 25.78, 29.46, 38.23, 38.55, 40.22, 50.49, 65.07, 65.49, 66.17, 68.99, 97.88, 110.12; exact mass, *m/z* calcd for $\mathrm{C_{23}H_{47}NO_5Si_2}$ 473.2993, found 473.2998. Anal. Calcd for $\mathrm{C_{23}H_{47}NO_5Si_2}$: C, 58.28; H,.10.00; N, 2.96. Found: C, 58.32; H, 9.87; N, 2.98.

N-[(4aα,5β,8α,8aα)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-oxo-1*H*-2-benzopyran-8-yl] trifluoroacetamide (269).



267 268 269

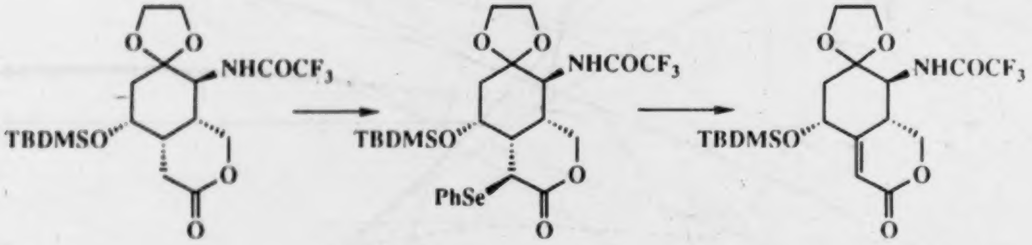
(a) ***N*-[(3α,4aβ,5α,8β,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-[[triethylsilyl]oxy]-1*H*-2-benzopyran-8-yl] trifluoroacetamide (268).** Trifluoroacetic anhydride (114 mg, 76 μl, 0.542

mmol) was injected dropwise over 30 sec into a cold (- 30 °C) and stirred solution of **267** (171 mg, 0.361 mmol) and 4-(dimethylamino)pyridine (*ca* 5 mg) in dry pyridine (0.9 mL). The mixture was stirred at -30 °C for 15 min, and 10% w/v aqueous copper sulfate (2 mL) and then ether (15 mL) were added. The organic layer was washed with 10% w/v aqueous copper sulfate (1 x 2 mL), and water (2 x 3 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (15 x 150 mm) using 20-40% ethyl acetate--hexane afforded **268**. A small amount (*ca* 5-10 mol%) of the corresponding lactols **268'** was also produced and this material was combined with **268** for the next step. Compound **268** had: FT-IR ($CHCl_3$ cast) 3300, 1712, 1560, 1081 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6 H), 0.57--0.67 (m, 6 H), 0.86 (s, 9 H), 0.90--0.99 (m, 9 H), 1.43--1.54 (m, 2 H), 1.73--1.89 (m, 3 H), 2.09--2.18 (dm, J = 13 Hz, 1 H), 3.45 (dd, J = 12.0, 2.4 Hz, 1 H), 3.76--3.88 (m, 2 H), 3.90--4.06 (m, 4 H), 4.53 (t, J = 10.8 Hz, 1 H), 4.67 (dd, J = 9.2, 2.4 Hz, 1 H), 5.98 (broad d, J = 10.0 Hz, 1 H).

(b) *N*-[(4aα,5β,8α,8aα)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-oxo-1*H*-2-benzopyran-8-yl] trifluoroacetamide (269). Celite (130 mg) and then pyridinium chlorochromate (230 mg, 1.06 mmol) were added to a stirred solution of **268** (194 mg, from above experiment) and **268'** (15 mg) in dry dichloromethane (3.0 mL). The mixture was stirred at room temperature for 2 h and then at 35 °C for 4 h, and allowed to cool to room temperature. Flash chromatography of the mixture (no work-up) over silica gel (20 x 150 mm) using 30% and then 50% ethyl acetate--hexane gave **269** (151 mg, 85% from amine **267**) as a white solid: FT-IR ($CHCl_3$ cast) 3280, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 6 H), 0.89 (s, 9 H), 1.85 (dd, J = 14.0, 9.8 Hz, 1 H), 1.94 (dd, J = 14.0, 4.8 Hz, 1 H), 1.99--2.07 (dm, J = 12.0 Hz, 1 H), 2.48--2.56 (m, 1 H), 2.61--2.69 (m, 2 H), 2.83--3.90 (m, 1 H), 3.94--

4.09 (m, 4 H), 4.22–4.30 (m, 2 H), 4.39 (dd, J = 11.8, 9.8 Hz, 1 H), 6.14 (broad d, J = 9.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ ; exact mass, *m/z* calcd for $C_{15}H_{21}F_3NO_6Si$ $(M - C_4H_9)^+$ 396.1091, found 396.1088.

N-[(5α,8β,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)-3,5,6,7,8,8a-hexahydro-3-oxo-1*H*-2-benzopyran-8-yl] trifluoroacetamide (271).



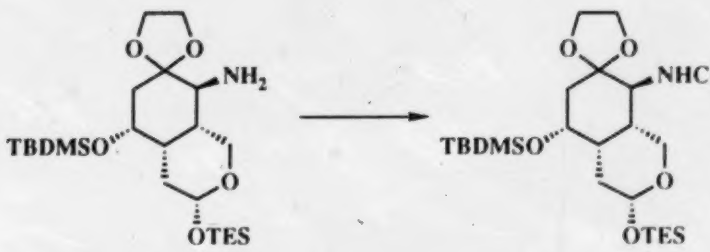
269 **270** **271**

(a) *N*-[(4α,4aα,5β,8α,8aα)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-oxo-4-(phenylseleno)-1*H*-2-benzopyran-8-yl] trifluoroacetamide (270). Compound **269** (49 mg, 0.107 mmol) was first dissolved in warm, dry THF and then the solution was cooled to -78 °C. To this cold (-78 °C) and stirred mixture, a cold (-78 °C) solution of LDA (0.25 M in THF, 1.28 mL, 0.321 mmol) was added over 15 sec followed by dry HMPA (180 μL). The cold bath was removed, the mixture was allowed to attain 0 °C (*ca* 10 min) and was then stirred at that temperature for 30 min, and then cooled to -78 °C again, at which point and benzeneselenyl bromide (0.77 M in THF, 0.95 mL, 0.749 mmol) was injected rapidly (*ca* 2 sec). The resulting solution was stirred at -78 °C for 10 min, quenched with saturated aqueous sodium bicarbonate (4 mL), and diluted with ether (15 mL). The organic layer was washed with 10% w/v aqueous copper sulfate (1 x 4 mL), water (1 x 4 mL), and dried ($MgSO_4$). Evaporation of the solvent left a brown-orange residue which was washed with a little hexane in order to remove most of the diphenyl diselenide present. Flash chromatography of the remaining yellowish solid over silica gel (15 x 150 mm) using first 5% ethyl acetate--hexane and then 35% ethyl acetate--hexane gave **270** (42 mg, 64%) as a white solid.

(b) *N*-[(5α,8β,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)-3,5,6,7,8,8a-hexahydro-3-oxo-1*H*-2-benzopyran-8-yl] trifluoroacetamide (271). Pyridine (70 μL, 0.885 mmol) and then 30% w/w aqueous hydrogen peroxide[#] (0.20 mL, 1.77 mmol) were added to a stirred solution of **270** (95 mg, 0.156 mmol) in 1.5:1 THF--dichloromethane (6 mL). The mixture was stirred for 3 h at room temperature and diluted with ethyl acetate (20 mL). The organic layer was washed with 10% w/v aqueous sodium bisulfite (1 x 4 mL), 10% w/v aqueous copper sulfate (1 x 4 mL), and water (1 x 4 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 x 150 mm) using 35% ethyl acetate--hexane gave **271** (64.5 mg, 92%) as a white solid: FT-IR ($CHCl_3$ cast) 3350, 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.11 (s, 6 H), 0.93 (s, 9 H), 1.76 (dd, J = 13.8, 12.4 Hz, 1 H), 2.23 (dd, J = 13.8, 5.6 Hz, 1 H), 2.68--2.78 (m, 1 H), 3.88--3.94 (m, 1 H), 4.02--4.18 (m, 4 H), 4.22 (dd, J = 12.2, 8.2 Hz, 1 H), 4.38--4.45 [m, including dd (J = 12.2, 8.2 Hz) at δ 4.42, 2 H], 6.18 (t, J = 2.0 Hz, 1 H), 6.45--6.52 (broad d, J = 8.2 Hz, 1 H); ^{13}C NMR (CD_3COCD_3, 106.6 MHz) δ -4.94, -4.75, 18.4, 26.09, 36.82, 43.81, 55.22, 55.30, 66.56, 66.60, 67.76, 69.46, 108.16, 113.63, 160.80, 163.92; exact mass, *m*/*z* calcd for $C_{19}H_{28}F_3NO_6Si$ 451.1639, found 451.1639. Anal. Calcd for $C_{19}H_{28}F_3NO_6Si$: C, 50.54; H, 6.25; N, 3.10. Found: C, 50.54; H, 6.47; N, 2.98.

[#] See caution in reference 67

(3α,4aβ,5α,8β,8aβ)-8-(*N*-Chloroamino)-5-[[dimethyl(1,1-dimethylethyl)-silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-[[triethylsilyl]oxy]-1*H*-2-benzopyran (276).



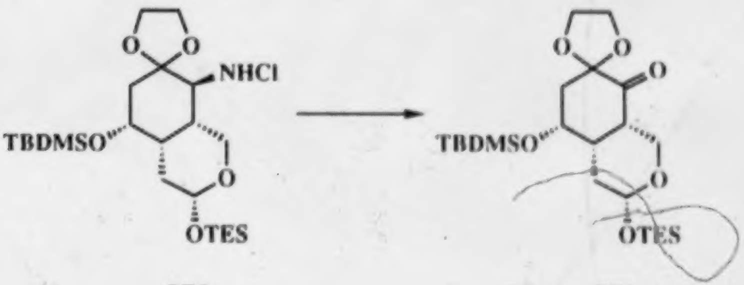
267 **276**

As *tert*-butyl hypochlorite is rather light sensitive, the reaction mixture as well as the solution of the reagent should be protected from light using aluminum foil. The reaction should also be closely monitored (TLC) and stopped a little short of completion to minimize bis-chlorination.# A solution of freshly prepared *tert*-butyl hypochlorite (94 mg, 0.87 mmol) in dry ether (2 mL) was added over 20 min (syringe pump) to a cold (- 45 °C) and vigorously stirred solution of **267** (303 mg, 0.64 mmol) in 1:2 THF--ether (6 mL). The cold bath was removed and the mixture was allowed to reach room temperature (15 min). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 x 150 mm) using 6--10% ethyl acetate--hexane gave **276** (250 mg, 77%) as a colorless oil: ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.03 (s, 6 H), 0.64 (q, J = 7.8 Hz, 9 H), 0.86 (s, 9 H), 0.96 (t, J = 7.8 Hz, 9 H), 1.41 (dt, J = 13.8, 10.0 Hz, 1 H), 1.62--1.81 (m, 3 H), 1.82 (ddd, J = 13.8, 4.0, 1.8 Hz, 1 H), 2.09--2.20 (m, 1 H), 3.40 (dd, J = 12.0, 4.0 Hz, 1 H), 3.45 (dd, J = 12.0, 2.4 Hz, 1 H), 3.91--4.07

# If some bischlorinated coumpound is obtained, it can be reconverted into **267** by dissolving it in ether and washing the resulting solution with 10% w/v aqueous sodium bisulfite

(m, 3 H), 4.08--4.19 (m, 2 H), 4.37 (dd, J = 12.4, 0.8 Hz, 1 H), 4.50--4.57 (broad d, J = 4.2 Hz, 1 H), 4.69 (dd, J = 9.4, 2.2 Hz, 1 H); exact mass, *m/z* calcd for $C_{21}H_{41}{}^{35}ClNO_5Si_2$ 478.2212, found 478.2189.

(3α,4aβ,5a,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-[[triethylsilyl]oxy]-8*H*-2-benzopyran-8-one (278).

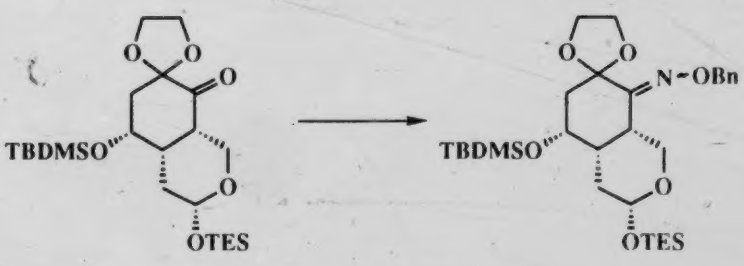


276 **278**

1,8-Diazabicyclo[5.4.0]undecane (0.368 mL, 2.46 mmol) was added to a stirred solution of **276** (250 mg, 0.493 mmol) in dry toluene (15 mL). The mixture was lowered into an oil bath and allowed to reach reflux temperature over 20 min. The mixture was refluxed for 40 min and then cooled to room temperature. Saturated aqueous ammonium chloride (10 mL) was added and stirring was continued at room temperature for 15 min in order to hydrolyse the imine. The mixture was diluted with ether (25 mL), and the organic layer was washed with 10% w/v aqueous copper sulfate (2 x 10 mL), and water (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (15 x 150 mm) using 20--30% ethyl acetate--hexane gave **278** (202 mg, 87%) as a colorless oil: FT-IR ($CHCl_3$ cast) 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 6 H), 0.62 (q, J = 8.0 Hz, 6 H), 0.88 (s, 9 H), 0.94 (t, J = 8.0 Hz, 9 H), 1.18 (dt, J = 13.8, 9.0 Hz, 1 H), 1.92--1.98 (dm, J = 13.0 Hz, 1 H), 2.03 (ddd, J = 14.0, 5.0, 1.6 Hz, 1 H), 2.19 (dd, J = 13.8, 12.0

Hz, 1 H), 2.36--2.44 (m, 1 H), 2.56--2.60 (m, 1 H), 3.35 (dd, J = 11.8, 3.0 Hz, 1 H), 3.72--3.77 (m, 1 H), 3.95--4.07 (m, 1 H), 4.12--4.18 (m, 1 H), 4.43 (dt, J = 12.0, 4.6 Hz, 1 H), 4.52 (dd, J = 12.0, 1.0 Hz, 1 H), 4.62 (dd, J = 9.0, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 106.6 MHz) δ -4.87, -4.71, 4.99, 6.69, 18.00, 25.71, 30.81, 39.77, 41.91, 42.65, 62.54, 64.44, 66.05, 67.48, 97.22, 104.66, 202.24; exact mass, *m*/*z* calcd for $C_{21}H_{39}O_6Si_2$ (M -C_2H_5) 443.2285, found 443.2275. Anal. Calcd for $C_{23}H_{44}O_6Si_2$: C, 58.43; H,.9.38 Found: C, 58.45; H, 9.23.

(3α,4aβ,5a,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)octahydro-3-[[triethylsilyl]oxy]-8*H*-2-benzopyran-8-one *O*-benzyl oximes (279a and 279b).

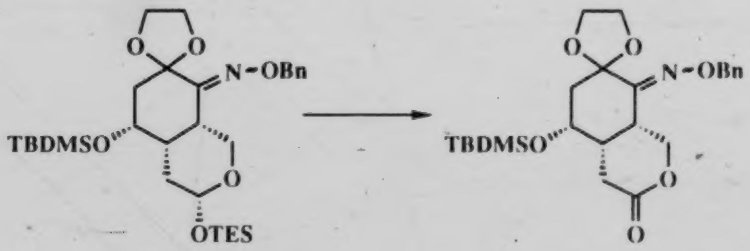


278 **279a** and **279b**

O-Benzylhydroxylamine hydrochloride (280 mg, 1.76 mmol) and powdered molecular sieves 4Å (50 mg) were added to a stirred solution of **278** (144 mg, 0.3 mmol) in absolute ethanol (6 mL) and pyridine (0.1 mL). The mixture was stirred at room temperature for 3 h and was then diluted with ether (50 mL). The resulting mixture was washed with 10% w/v aqueous copper sulfate (2 x 5 mL), and water (1 x 5 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (10 x 150 mm) using 10% ethyl acetate--hexane gave **279a** and **279b** (133 mg, 75%) as a gummy solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s) and 0.07

(s) [both signals together correspond to 6 H], 0.54--0.75 (m, 6 H), 0.88 (s, 9 H), 0.92--1.03 (m, 9 H), 1.17--1.43 (m, 0.67 H), 1.62--2.25 (m, 4 H), 2.32--2.40 (m, 0.67 H), 2.94 (dd, 11.2, 5.0 Hz, 0.33 H), 3.42 (dd, 11.8, 3.3 Hz, 0.67 H), 3.55--4.15 (m, *ca* 3.67 H), 4.16 (dt, J = 12.0, 5.3 Hz, 0.67 H), 4.41 (dd, J = 12.0, 5.3 Hz, 0.33 H), 4.52 (d, J = 11.5 Hz, 0.67 H), 4.70 (dd, J = 9.0, 2.0 Hz, 0.67 H), 4.90 (dd, J = 8.7, 3.8 Hz, 0.33 H), 5.03--5.21 (m, 2 H), 7.25--7.47 (m, 5 H); exact mass, m/z calcd for $C_{30}H_{51}NO_6Si_2$ 577.3254, found 577.3247.

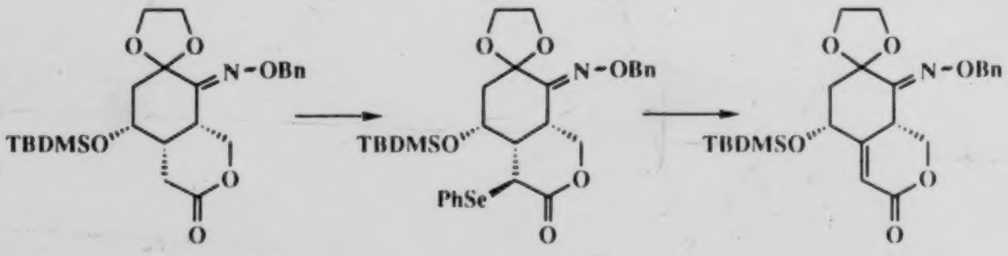
(4aα,5β,8aα)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)tetrahydro-1*H*-2-benzopyran-3,8-(4*H*,7*H*)-dione *O*-benzyl oximes (280a and 280b).



279a and **279b** **280a** and **280b**

Pyridinium chlorochromate (194 mg, 0.9 mmol) and powdered molecular sieves 4Å (50 mg) were added to a stirred solution of **279a** and **279b** (130 mg, 0.225 mmol) in dry dichloromethane (5 mL). The mixture was stirred for 16 h at room temperature. Flash chromatography (no work-up) of the mixture on silica gel (20 x 180 mm) using ethyl acetate--hexane 30--40% gave **280a** and **280b** (94 mg, 90 %) as a white semi-solid: FT-IR ($CHCl_3$ cast) 1737 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.6 (s) and 0.7 (s) and 0.8 (s) and 0.9 (s) [all signals together correspond to 6 H], 0.87 (s) and 0.89 (s) [all signals together correspond to 9 H], 1.97 (dd, J = 14.4, 5.0 Hz, 1 H), 2.14 (dd, J = 14.4, 9.6 Hz, 1 H), 2.20 (d, J = 4.6 Hz, 1 H), 2.30 (dd, J = 17.6, 12.0 Hz, including m at δ 2.26--2.31, 1.35 H), 2.48--2.68 (m, 2.0 H), 2.92 (dd, J = 8.6, 4.2 Hz, 0.66 H), 3.59--3.72 (m, 1 H), 3.84--4.0 (m, 3.33 H), 4.12--4.22 (m, 1 H), 4.24--4.30 (m, 1 H), 4.74 (dd, J = 11.6, 3.8 Hz, 0.66 H), 4.82 (dd, J = 10.4, 12.0 Hz, 0.33 H), 5.08 (dd, J = 16.8, 12.0 Hz, 1.34 H), 5.15 (s, 0.66 H), 7.27--7.40 (m, 5.0 H); ^{13}C NMR (CDCl$_3$, 106.6 MHz) δ -5.09, -4.90, -4.68, -4.52, 17.66, 17.92, 25.66, 27.23, 31.64, 32.24, 35.95, 36.36, 37.72, 41.23, 41.76, 64.13, 64.19, 65.00, 65.46, 67.15, 67.98, 68.50, 69.53, 76.63, 77.45, 104.31, 105.10, 127.96, 128.11, 128.35, 128.39, 128.46, 128.55, 137.37, 137.47, 150.02, 153.21, 170.14, 170.60; exact mass, *m*/*z* calcd for $C_{24}H_{35}NO_6Si$ 461.2234, found 461.2231. Anal. Calcd for $C_{24}H_{35}NO_6Si$: C, 62.44; H,.7.64; N, 3.03 Found: C, 62.22; H, 7.46; N, 2.95.

(5α,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)-5,6,7,8-tetrahydro-3*H*-2-benzopyran-3,8-dione O-benzyl oximes (282a and 282b).

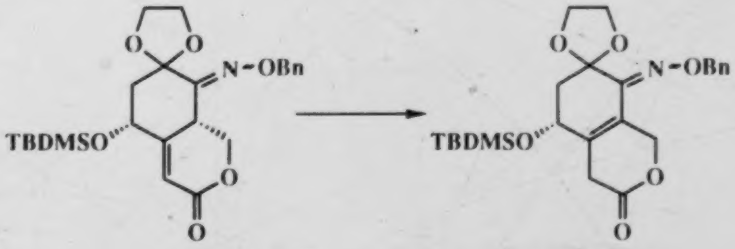


280a and **280b** **281a** and **281b** **282a** and **282b**

(a) (4α,4aα,5β,8aα)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)-tetrahydro-4-(phenylseleno)-1*H*-2-benzopyran-3,8-(4*H*,7*H*)-dione *O*-benzyl oximes (281a and 281b). A cold (-78 °C) solution of LDA (0.25 M in THF, 0.728 mL, 0.182 mmol) was added over 15 sec to a cold (-78 °C) and stirred solution of **280a** and **280b** (70 mg, 0.151 mmol) in dry THF (2 mL). The mixture was stirred at -78 °C for 1.5 h. A solution of benzeneselenyl bromide (0.77 M in THF, 0.273 mL, 0.21 mmol) [prepared by adding bromine (20 μL, 0.39 mmol) to a vigorously stirred solution of diphenyl diselenide (135 mg, 0.43 mmol) in dry THF (1 mL)] was injected rapidly (2 sec) to the cold solution. After being stirred at -78 °C for 15 min, the mixture was quenched with saturated aqueous sodium bicarbonate (1 x 4 mL), and diluted with ether (15 mL). The organic layer was washed with water (1 x 4 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the yellowish, solid residue over silica gel (15 x 150 mm) using 10% ethyl acetate--hexane gave **281a** and **281b** (74 mg, 79%) as a slightly yellow oil.

(b) (5α,8aβ)-5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)-5,6,7,8-tetrahydro-3*H*-2-benzopyran-3,8-dione O-benzyl oximes (282a and 282b). Dimethyldioxirane[68] (0.020 M in acetone, 5 mL, 0.10 mmol) was added over 1 min to a cold (- 78 °C) and stirred solution of **281a** and **281b** (38 mg, 0.062 mmol) in dichloromethane (0.5 mL). The cold bath was removed and the mixture was allowed to reach room temperature (30 min). The mixture was then diluted with ether (15 mL) and washed with saturated aqueous sodium bicarbonate (2 x 4 mL), and brine (1 x 4 mL) and dried ($MgSO_4$). Evaporation of the solvent gave **282a** and **282b** (30 mg, *ca* 100%) as a colorless oil that > 95% pure [^{1}H NMR (400 MHz)]: FT-IR ($CHCl_3$ cast) 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s) and0.12 (s) [both signals together correspond to 6 H], 0.90 (s) and 0.93 (s) [both signals together correspond to 9 H), 2.04--2.13 (m, 1 H), 2.20 (dd, J = 15.2, 6.0 Hz, 0.5 H), 2.74 (dd, J = 14.0, 9.6 Hz, 0.5 H), 3.52--3.58 (m, 1 H), 3.73--3.80 (m, 0.5 H). 3.92--4.00 (m, 3 H), 4.10--4.21 (m, 2 H), 4.38--4.44 (tm, J = 9.0 Hz) and 4.44 (dd, J = 12.0, 9.0 Hz), 4.53--4.61 (m, 1.0 H), 4.61--4.67 (ddm, J = 11.6, 6.0 Hz, 0.5 H), 5.07 (dd, J = 16.0, 12.0 Hz, 1 H), 5.17 (s, 1 H), 6.12 (t, J = 2.2 Hz, 0.5 H), 6.15 (t, J = 2.2 Hz, 0.5 H), 7.29--7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 106.6 MHz) δ -5.00, -4.91, -4.80, 18.16, 25.73, 25.76, 34.31, 37.49, 44.36, 44.54, 63.86, 64.71, 65.75, 65.88, 65.95, 67.04. 67.10, 68.18, 77.37, 77.72, 104.89, 104.97, 112.70, 113.18, 128.16, 128.41, 128.50, 128.60, 136.80, 137.11, 149.46, 150.30, 159.58, 160.25, 163.76, 164.29; exact mass, *m*/*z* calcd for $C_{20}H_{24}NO_6Si$ 402.1373, found 402.1389.

5-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-7,7-(ethylenedioxy)-5,6-dihydro-1*H*-2-benzopyran-3,8-(4*H*,7*H*)-dione *O*-benzyl oximes (283a and 283b).



282a and **282b** **283a** and **283b**

When **282a** and **282b** is subjected to flash chromatography, it isomerizes almost completely to **283a** and **283b**: FT-IR ($CHCl_3$ cast) 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s) and 0.14 (s) [both signals together correspond to 6 H], 0.89 (s) and 0.91 (s) [both signals together correspond to 9 H), 2.08 (dd, J = 10.0 Hz, 0.3 H), 2.18 (dd, J = 13.0, 9.4 Hz, including a multiplet at 2.14--2.19, 1.0 H), 2.35 (dd, J = 13.0, 6.0 Hz, 0.70 H), 2.97--3.26 (m, *ca* 1.70 H), 3.42---3.49 (m, *ca* 0.3 H), 3.75--4.18 (m, 4 H), 4.42--4.51 (m, 1 H), 5.05--5.09 (m, 0.5 H), 5.09--5.18 (m, 2 H), 5.20--5.25 (m, *ca* 1.25 H), 7.30--7.40 (m, 5 H); exact mass, *m*/*z* calcd for $C_{20}H_{24}NO_6Si$ 402.1375, found 402.1372.

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APPENDIX 1

X-RAY CRYSTAL STRUCTURE OF THE 3,5-DINITROBENZOATE DERIVATIVE OF 34

EXPERIMENTAL

Data Collection

A clear, colorless, thin crystal of $C_{17}H_{16}N_2O_8$, with the approximate dimensions of 0.057 × 0.240 × 0.270 mm, was mounted on a glass fiber with epoxy, and optically centered in the x--ray beam of an Enraf-Nonius CAD4 automated diffractometer. The prominent face was the [100], and the two smaller faces were the [010] and [001] faces. The crystal was cooled to approximately -20C, using a cold air stream apparatus, and all measurements were made at this temperature. All intensity measurements were performed using Mo Kα radiation (λ = 0.7107 Å) with a graphite crystal, incident beam monochromator.

The automatic peak search and reflection indexing programs[1] generated a monoclinic cell. The systematic absences of h0l, l odd, 0k0, k odd, and the magnitude of the unit cell volume led to the unique choice of space group as $P2_1/c$ (No.~14)[2] The cell constants and orientation matrix were obtained from a least-squares refinement of the setting angles of 25 reflections in the range $7.8<\theta<14.8^o$. The unit cell parameters are given in Table 1.

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[1] The diffractometer programs are those supplied by Enraf-Nonius for operating the operating the CAD4F diffractometer; some local modifications by Dr. R. G. Ball.

[2] *International Tables for X-Ray Crystallography* (1969). Vol. I. Birmingham: Kynoch Press.

The intensity data were collected with θ–2θ scans at fixed speed, $5.0^{\circ}\mathrm{min}^{-1}$ (in θ). The scan range was varied as a function of θ to compensate for the α_1–α_2 wavelength dispersion: ω scan width = $1.00 + 0.347\tan\theta$.

The backgrounds for the peaks were measured by extending the scan 25% on each side of the calculated range; this gave a peak--to--background counting time ratio of 2:1. The crystal did not diffract well, and the intensity measurements were made out to a maximum 2θ of 40°. Three reflections were chosen as standard reflections, and were remeasured after every 120 min of exposure time to check on crystal and electronic stability over the course of data collection. There was a change in intensity of roughly ±4% over the time span of data collection. This was considered negligible, and no decay correction was used. Several other crystals were examined, but there was no significant diffraction beyond the $2\theta = 40^{\circ}$ limit. (Only about 5% of the reflections at higher angle had intensities greater than three times their estimated standard deviations.)

Data Reduction

A total of 4167 reflections were collected, and Lorentz and polarization factors were applied: $I = r(S - 2B)/Lp$ and $\sigma_I = [r(S + 4B) + (0.04I)^2]^{1/2}/Lp$, where r is the scan rate, S is the total scan count, B is the total background count, and Lp is the combined Lorentz and polarization factor.

Structure Solution and Refinement

The structure was solved using the direct methods program MITHRIL[3] \ref{.}, in which all 27 non-hydrogen atoms were located; R began at 0.18.

Adjustment[4] of atomic parameters was carried out by full--matrix least--squares refinement on F_o minimizing the function $\Sigma|F_o|-|F_c|)^2$ where $|F_o|$'s and $|F_c|$ are the observed and calculated structure factor amplitudes and the weight is $4F_o{}^2/\sigma^2(F_o{}^2)$. The neutral atom scattering factors were calculated from the analytical expression for the scattering factor curves[5] .The f' and f'' components of anomalous dispersion[6] were included in the calculations of all non-hydrogen atoms.

The hydrogen atoms were generated at idealized calculated positions by assuming a C--H bond length of 0.95Å and the appropriate sp^2 or sp^3 geometry. The positions of the hydrogen atoms on the C(19) methyl group were generated a by least--squares refinement of the coordinates derived from a difference Fourier map. The hydrogen atoms were then included in the calculations with fixed, isotropic Gaussian parameters 1.2 times that of the attached atom and constrained to `ride' on the attached atom. The refinement of the coordinates and isotropic U's for all non--hydrogen atoms was continued to convergence. At that stage, the data were corrected for absorption by use of an empirical scheme based on the absorption surface (Fourier filtering) method of Walker and Stuart[7]. The maximum and minimum correction factors applied to F_o were 1.4320 and 0.7325. After averaging over 2/m symmetry (R-merge on F is 0.096) and deleting the systematic absences, there were 1719 averaged reflections, 1004 with $I > \sigma_I$. In the final cycle, 244 parameters were refined with the 1004 observations having $I > \sigma_I$ and the largest and and average shift/error ratio in the final cycle was less than 0.01. As a result, the final goodness--of--fit was 1.39, and $R_1 = \Sigma||Fo|-||Fc|||/\Sigma|Fo| = 0.072$, $R_2 = \Sigma\, w(|Fo|-|Fc|)2/\Sigma\, wFo^2)^{1/2} = 0.064$. An analysis of R_2 in terms of Fo, $\sin\theta/\lambda$, various combinations of (h, k, l) indicated no unusual trends. The highest peak in the final difference Fourier map has a density of 0.30(7) e Å^{-3}

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[3] Gilmore, C. J. (1983). *MITHRIL* 83. A Multiple Solution Direct Methods Program. University of Glasgow

[4] The computer programs used in this analysis include the Enraf-Nonius Structure Determination Package. Version 3 (1985, Delft, The Netherlands) adapted for a SUN Microsystems 3/160 computer, and several locally written programs by Dr. R. G. Ball

[5] *International Tables for X-Ray Crystallography* (1974). Vol. IV. Table 2.2B. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

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Table 1. Experimental Details

A. Crystal Data

$C_{17}H_{16}N_2O_8$	FW = 376.33
Crystal dimensions:	0.057 × 0.240 × 0.270 mm
monoclinic space group	$P2_1/c$

$a=16.454(8)$, $b=14.693(6)$, $c=7.266(3)$ Å, $\beta=91.88(4)^{\circ}$

$V = 1755$ Å^3; $Z = 4$; $D_c = 1.421$ g cm^{-3}; $\mu = 1.08$ cm^{-1}

B. Data Collection and Refinement Conditions

Radiation:	Mo Kα, $\lambda = 0.7107$ Å
Monochromator:	incident beam, graphite crystal
Take-off angle:	3.00°
Detector aperture:	2.40 mm horiz × 4.0 mm vert
Crystal-to-detector distance:	205 mm
Scan type:	$\theta - 2\theta$
Scan rate:	5.0°min^{-1}
Scan width:	$1.00 + 0.347\tan\theta$
Data collection 2θ limit:	40°
Data collection index range:	$+h,+k,\pm l$
Number of Reflections:	1719 total, averaged; 1004 with $I>\sigma_I$
Observations:variables ratio:	1004: 244
Agreement factors R_1, R_2, GOF:	0.072, 0.064, 1.39
Corrections applied:	empirical absorption surface

Table of Selected Interatomic Angles (in degrees)

Atom1	Atom2	Atom3	Angle
C2	C1	C6	117.4 (7)
C1	C2	N2	117.9 (7)
C1	C2	C3	124.6 (7)
N2	C2	C3	117.6 (6)
C2	N2	O21	118.2 (6)
C2	N2	O22	118.8 (6)
O21	N2	O22	122.9 (6)
C2	C3	C4	114.6 (6)
C3	C4	N4	116.5 (6)
C3	C4	C5	123.9 (7)
N4	C4	C5	119.6 (7)
C4	N4	O41	118.4 (6)
C4	N4	O42	117.0 (6)
O41	N4	O42	124.6 (7)
C4	C5	C6	118.3 (7)
C1	C6	C5	121.2 (7)
C1	C6	C7	121.5 (7)
C5	C6	C7	117.3 (6)
C6	C7	O7	125.7 (7)
C6	C7	O8	109.9 (6)
O7	C7	O8	124.4 (7)
C7	O8	C9	119.3 (6)
O8	C9	C10	107.2 (7)
O8	C9	C14	105.7 (6)
C10	C9	C14	114.5 (7)
C9	C10	C11	122.3 (8)
C10	C11	C12	122.3 (9)
C11	C12	C13	116.9 (7)
C11	C12	C15	116.6 (7)
C13	C12	C15	60.3 (6)
C12	C13	C14	118.1 (7)
C12	C13	C15	60.4 (5)
C14	C13	C15	122.6 (7)
C9	C14	C13	114.1 (7)
C12	C15	C13	59.3 (6)
C12	C15	C16	117.6 (7)
C13	C15	C16	117.2 (7)
C15	C16	O16	123.8 (7)
C15	C16	O17	111.1 (7)
O16	C16	O17	125.0 (8)
C16	O17	C18	116.5 (6)
O17	C18	C19	106.3 (7)

Table of Selected Bond Lengths (Å)

Atom1	Atom2	Length	Atom1	Atom2	Length
C1	C2	1.379 (10)	C2	N2	1.472 (10)
C2	C3	1.385 (11)	N2	O21	1.221 (9)
C3	C4	1.384 (10)	N2	O22	1.224 (8)
C4	C5	1.374 (10)	C4	N4	1.497 (10)
C5	C6	1.382 (10)	N4	O41	1.215 (8)
C6	C1	1.377 (10)	N4	O42	1.215 (9)
C6	C7	1.486 (10)	C7	O7	1.188 (10)
C7	O8	1.345 (10)	O8	C9	1.517 (9)
C9	C10	1.479 (13)	C9	C14	1.501 (12)
C10	C11	1.332 (12)	C11	C12	1.498 (13)
C12	C13	1.466 (13)	C12	C15	1.482 (11)
C13	C14	1.524 (11)	C13	C15	1.482 (11)
C15	C16	1.513 (11)	C16	O16	1.204 (10)
C16	O17	1.329 (10)	O17	C18	1.471 (10)
C18	C19	1.507 (13)			

Table of Hydrogen Atom Coordinates (×10^4) and U's (Å^2, ×10^4)

Atom	x	y	z	U
H1	6725	5960	5927	451
H3	4529	7234	6321	357
H5	4807	4604	7994	342
H9	7478	3087	6452	544
H10	7640	3223	9548	620
H11	8778	3882	10683	782
H12	9614	4507	9021	657
H13	9268	4542	5220	609
H141	8097	4172	4441	604
H142	8631	3375	5187	604
H15	8217	5711	7559	460
H181	9408	7934	6140	685
H182	9478	7955	8274	685
H191	8676	9174	7243	943
H192	8088	8493	6256	943
H193	8159	8514	8390	943

Table of Torsional Angles

C6	C1	C2	N2	177.24 (0.67)	C7	O8	C9	C14	163.64 (0.69)
C6	C1	C2	C3	-1.41 (1.16)	O8	C9	C10	C11	-94.00 (0.91)
C2	C1	C6	C5	2.55 (1.14)	C14	C9	C10	C11	22.98 (1.13)
C2	C1	C6	C7	179.97 (1.92)	O8	C9	C14	C13	78.54 (0.79)
C1	C2	N2	O21	17.07 (1.03)	C10	C9	C14	C13	-39.29 (0.93)
C1	C2	N2	O22	-161.29 (0.70)	C9	C10	C11	C12	3.39 (1.29)
C3	C2	N2	O21	-164.19 (0.68)	C10	C11	C12	C13	-11.79 (1.20)
C3	C2	N2	O22	17.45 (1.01)	C10	C11	C12	C15	56.70 (1.14)
C1	C2	C3	C4	-0.64 (1.10)	C11	C12	C13	C14	-6.78 (1.08)
N2	C2	C3	C4	-179.29 (0.67)	C11	C12	C13	C15	106.75 (0.82)
C2	C3	C4	N4	-177.33 (0.66)	C15	C12	C13	C14	-113.53 (0.80)
C2	C3	C4	C5	1.68 (1.13)	C11	C12	C15	C13	-107.31 (0.86)
C3	C4	N4	O41	-3.53 (1.06)	C11	C12	C15	C16	145.88 (0.77)
C3	C4	N4	O42	177.64 (0.70)	C13	C12	C15	C16	-106.81 (0.78)
C5	C4	N4	O41	177.42 (0.74)	C12	C13	C14	C9	31.85 (1.00)
C5	C4	N4	O42	-1.42 (1.11)	C15	C13	C14	C9	-39.30 (1.05)
C3	C4	C5	C6	-0.62 (1.18)	C12	C13	C15	C16	107.46 (0.80)
N4	C4	C5	C6	178.36 (0.69)	C14	C13	C15	C12	106.27 (0.88)
C4	C5	C6	C1	-1.61 (1.15)	C14	C13	C15	C16	-146.27 (0.76)
C4	C5	C6	C7	-179.13 (0.71)	C12	C15	C16	O16	28.39 (1.19)
C1	C6	C7	O7	178.91 (0.87)	C12	C15	C16	O17	-148.77 (0.72)
C1	C6	C7	O8	-2.52 (1.06)	C13	C15	C16	O16	-39.29 (1.16)
C5	C6	C7	O7	-3.57 (1.27)	C13	C15	C16	O17	143.55 (0.71)
C5	C6	C7	O8	174.99 (0.69)	C15	C16	O17	C18	177.60 (0.66)
C6	C7	O8	C9	-178.41 (0.64)	O16	C16	O17	C18	0.48 (1.21)
O7	C7	O8	C9	0.18 (1.06)	C16	O17	C18	C19	176.91 (0.72)
C7	O8	C9	C10	-73.74 (0.84)					

Table of Positional (× 10^4) and Anisotropic Gaussian Displacement Parameters (Å^2, × 10^3)

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O21	6676(3)	7471(4)	4545(8)	64(4)	67(3)	70(5)	1(3)	22(4)	25(4)
O22	5677(3)	8250(3)	5544(8)	76(4)	44(3)	70(5)	15(3)	9(4)	11(3)
O41	3291(3)	6578(4)	7421(9)	48(4)	71(4)	95(5)	13(3)	6(4)	0(4)
O42	3416(3)	5168(4)	8181(9)	57(4)	59(4)	126(6)	1(3)	28(4)	9(4)
O7	6098(3)	3644(3)	8002(9)	48(4)	45(3)	112(5)	3(3)	11(4)	20(4)
O8	7083(3)	4448(3)	6693(8)	44(3)	49(3)	81(5)	6(3)	12(4)	5(3)
O16	9919(3)	6284(4)	7065(10)	53(4)	85(4)	112(6)	-12(4)	-1(4)	-21(4)
O17	8715(3)	6986(4)	7335(7)	63(4)	63(4)	37(4)	-9(3)	-1(3)	-3(3)
N2	6030(4)	7527(4)	5317(9)	53(5)	65(4)	33(4)	11(4)	-1(4)	19(4)
N4	3685(4)	5884(4)	7623(10)	49(5)	54(4)	65(6)	1(4)	-5(4)	-3(4)
C1	6174(5)	5940(5)	6275(11)	39(5)	49(5)	33(6)	1(4)	-7(5)	0(5)
C2	5674(5)	6688(5)	6049(10)	54(5)	43(5)	16(5)	0(4)	-1(5)	6(4)
C3	4862(4)	6711(5)	6498(10)	42(5)	44(5)	15(5)	10(4)	-1(4)	-11(4)
C4	4569(4)	5904(5)	7198(11)	30(5)	56(5)	30(6)	-1(4)	0(4)	-11(5)
C5	5035(5)	5138(5)	7485(11)	45(5)	33(4)	37(5)	-7(4)	-5(5)	-12(4)
C6	5844(4)	5170(5)	7035(11)	21(4)	48(5)	34(5)	-4(4)	-4(4)	-9(5)
C7	6333(5)	4330(5)	7333(12)	48(6)	50(5)	61(7)	10(5)	4(5)	1(5)
C9	7686(5)	3667(5)	6804(12)	45(5)	43(5)	70(7)	5(4)	8(5)	6(5)
C10	7960(5)	3578(5)	8755(12)	87(7)	60(5)	50(6)	15(5)	24(6)	13(6)
C11	8631(6)	3983(5)	9424(14)	95(8)	57(6)	77(8)	15(6)	-5(7)	19(6)
C12	9135(5)	4599(5)	8279(13)	59(6)	61(6)	65(7)	17(5)	-24(6)	2(6)
C13	8956(5)	4602(5)	6290(12)	56(6)	73(6)	39(6)	-1(5)	7(5)	-9(5)
C14	8345(5)	3910(5)	5514(12)	48(6)	65(6)	58(7)	-8(5)	-1(5)	-19(6)
C15	8712(5)	5390(5)	7419(11)	48(5)	49(5)	29(5)	-3(5)	-9(5)	-12(5)
C16	9193(5)	6260(6)	7223(11)	63(6)	70(6)	25(6)	-4(5)	-14(5)	-10(5)
C18	9116(6)	7879(5)	7241(13)	65(6)	61(7)	-40(6)	-4(7)	2(6)	
			102(7)						
C19	8449(6)	8581(6)	7289(14)	55(6)	91(9)	-11(7)	2(8)	13(7)	
			129(9)						

The form of the AGDP is exp[$-2\pi^2(h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+l^{\wedge 2}c^{*2}U_{33}+2hka^*b^*U_{12}+2hla^*c^*U_{13}+2klb^*c^*U_{23})$]